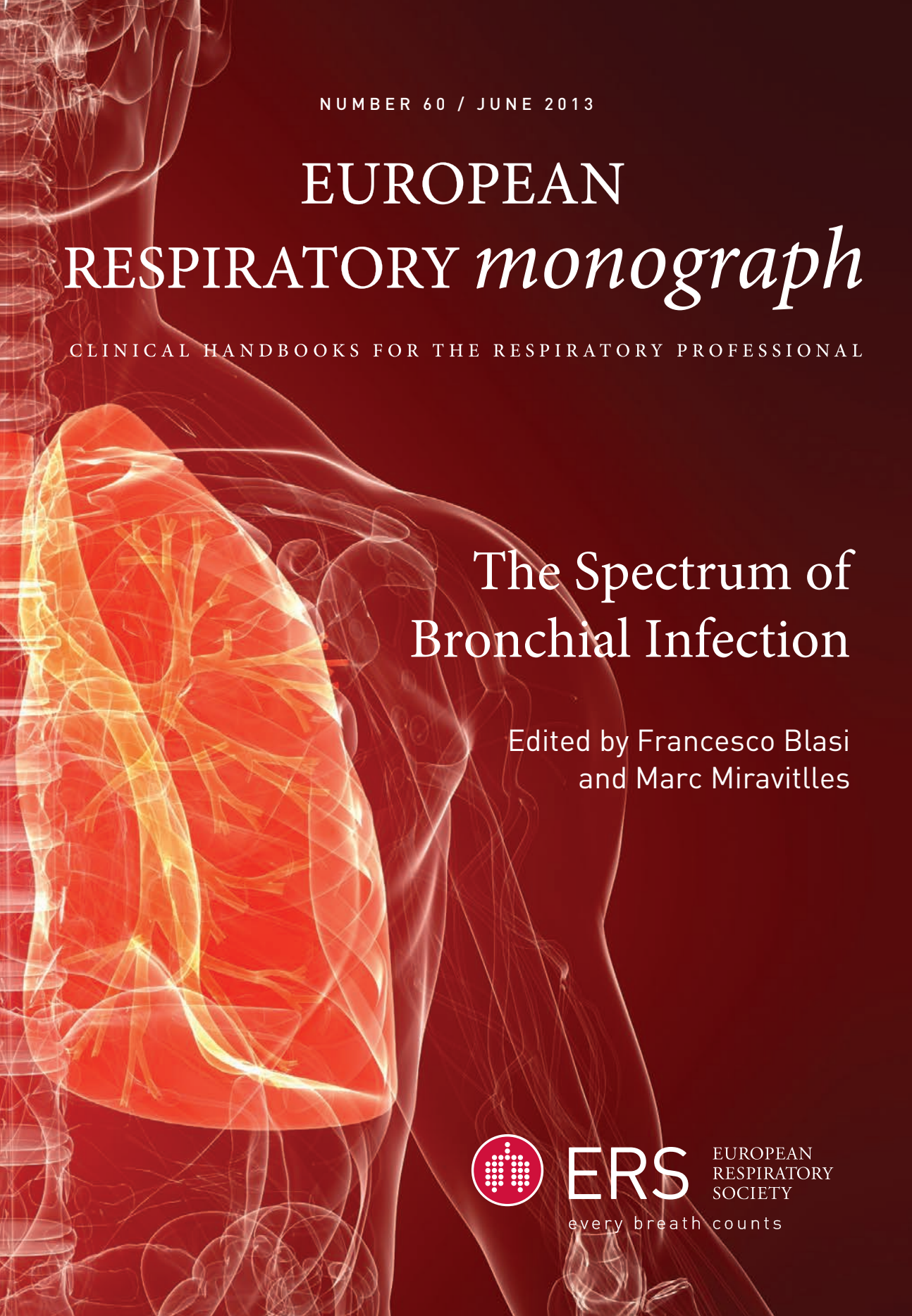
NUMBER 60 / JUNE 2013

EUROPEAN RESPIRATORY *monograph*

CLINICAL HANDBOOKS FOR THE RESPIRATORY PROFESSIONAL



The Spectrum of Bronchial Infection

Edited by Francesco Blasi
and Marc Miravitlles

ERS EUROPEAN RESPIRATORY SOCIETY
every breath counts

European Respiratory Monograph 60, June 2013

The Spectrum of Bronchial Infection

Edited by
Francesco Blasi and Marc Miravitlles

Editor in Chief
Tobias Welte

Published by European Respiratory Society ©2013
June 2013
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674
Printed by Page Bros Ltd, Norwich, UK

Managing Editor: Rachel White
European Respiratory Society
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S10 2PX, UK
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This book is one in a series of *European Respiratory Monographs*. Each individual issue provides a comprehensive overview of one specific clinical area of respiratory health, communicating information about the most advanced techniques and systems required for its investigation. It provides factual and useful scientific detail, drawing on specific case studies and looking into the diagnosis and management of individual patients. Previously published titles in this series are listed at the back of this *Monograph*.

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Preface

The 21st century will be described as the century of infectious diseases. This is not only because of the increasing number of new infections, such as severe acute respiratory syndrome, the H1N1 pandemic or the spread of West Nile virus and dengue fever, but also because the role of infection in the pathogenesis of chronic diseases has been recognised and is now better understood. Chronic bronchial infection plays a role in the progression and prognosis of many lung diseases but also contributes to a systemic inflammatory response, which is a predisposition for extrapulmonary diseases such as arteriosclerosis or diabetes mellitus.

At present, the mechanisms that contribute to chronic pathogenic colonisation of the lower respiratory tract are not entirely clear. Is there a defect of the innate or the adaptive immune system of the lung favouring chronic colonisation? Are there deficits in the innate and/or adaptive immune system on a local pulmonary level that contribute to the primary colonisation and secondary tissue damage? What is the role of air pollution and other environmental factors?

Many questions about chronic bronchial infection are unclear. Is it possible to prevent this condition by early, adequate treatment of the underlying disease or is it better to stimulate an immune response by vaccination or similar immunomodulatory agents? Is it possible to influence the course of the disease by treating chronic pulmonary infection? How long should the treatment period last for? Should the patient receive the same treatment strategy or should different treatment be administered at different time-points?

This issue of the *European Respiratory Monograph* (*ERM*) summarises the current understanding of chronic bronchopulmonary infections and addresses future needs.

I would like to congratulate the Guest Editors, Francesco Blasi and Marc Miravitlles, for their tremendous work in bringing together this cutting-edge *ERM*, which should be of interest for general medical doctors and respiratory physicians, as well as infectious diseases specialists. In addition, it will provide guidance for future basic and clinical research. I am sure that readers from different areas of respiratory medicine will find this *ERM* useful in their daily practice.

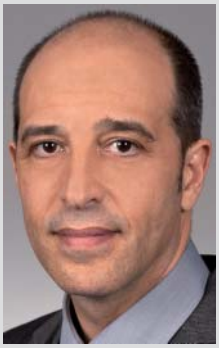
Eur Respir Monogr 2013; 60: v. Copyright ERS. DOI: 10.1183/1025448x.10005813. Print ISBN: 978-1-84984-034-7. Online ISBN: 978-1-84984-035-4. Print ISSN: 1025-448x. Online ISSN: 2075-6674.

Guest Editors

Francesco Blasi

Francesco Blasi is Professor of Respiratory Medicine and Vice-chairman of the Department of Pathophysiology and Transplantation at the University of Milan, Milan, Italy, as well as Director of Respiratory Diseases at the Unit IRCCS Fondazione Cà Granda Ospedale Maggiore Milan. He is currently President of the European Respiratory Society (ERS) (2012–2013).

Professor Blasi has published more than 180 papers in international journals. He is an Associate Editor on the editorial boards of *Pulmonary Pharmacology and Therapeutics*, *Respiratory Research*, *Clinical Respiratory Journal* and *Therapeutic Advances in Respiratory Disease*. His research interests include the effects of atypical bacterial infection on cellular immunity in chronic bronchitis, and the role of atypical bacteria and viral infection in asthma onset. He is also interested in the role of antibiotics in the treatment of chronic obstructive pulmonary disease (COPD) exacerbations and asthma. He is actively working on pneumonia and tuberculosis research trials. Professor Blasi was also involved in the ERS/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines on lower respiratory tract infections. In addition to being a member of the ERS, he is also a member of the American Thoracic Society (ATS) and the Italian Respiratory Medicine Society (SIMeR).



Marc Miravitlles

Marc Miravitlles is a pulmonologist working in clinical research in the Hospital Universitari Vall d'Hebron in Barcelona, Spain. His primary research interests include COPD, chronic bronchitis, α_1-antitrypsin deficiency, lung defence mechanisms and respiratory infections.

Marc Miravitlles serves on various medical committees and is a member of numerous professional societies, including the Spanish Society of Pneumology and Thoracic Surgery (SEPAR), where he served as Secretary (1999–2003), and was responsible for international relationships from 2006 to 2011. Dr Miravitlles acted as the Chair of the Respiratory Infections Group of the ERS (2008–2011). He has also acted as a consultant for the development of different international guidelines for COPD, such as the ATS/ERS Task Force on outcomes in COPD. He was also a consultant of the Spanish Ministry of Health for the development of the national strategy against COPD (2009 onwards) and is the coordinator of the Spanish national guidelines for COPD. Dr Miravitlles is Editor in Chief of *Hot Topics in Respiratory Medicine*, Editor in Chief of *Therapeutic Advances in Respiratory Diseases* and serves as an Associate Editor for *Respiration*, the *International Journal of COPD* and the *Clinical Respiratory Journal*. Dr Miravitlles has published over 200 articles in a number of peer-reviewed international medical journals, which were largely related to COPD, infection in COPD and α_1-antitrypsin deficiency.

Eur Respir Monogr 2013; 60: vii.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10005213
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Introduction

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Optimistically, by the middle of the last century there was the idea that the battle against infections would be won. However, it soon became evident that the mechanisms of adaptation of bacteria to new conditions, including the widespread use of antibiotics, would help them to survive even in hostile environments. Now, it is clear that the battle continues and that the advances of treatments in other areas have changed the battlefield.

This is particularly true in respiratory infections. The different forms of pneumonia are still a clinical challenge and their mortality is still significant in the elderly or immunosuppressed, but other forms of respiratory infections are responsible for a great burden of disease. In particular, infections of the bronchial tree, which include a spectrum of clinical manifestations from benign acute bronchitis in otherwise healthy individuals, to severe exacerbations of patients affected by chronic obstructive pulmonary disease (COPD) or bronchiectasis that are probably the most frequent types of infections in adults. It is no exaggeration to say that everybody has suffered some (or several) form(s) of bronchial infection, fortunately most of them are self-limited, but even the milder forms represent a major cause of morbidity, use of healthcare resources and work absenteeism. The major pathogens involved are the respiratory viruses and bacteria such as *Haemophilus influenzae, Streptococcus pneumoniae* and *Pseudomonas aeruginosa*, among others. The aetiological agents will vary depending on the characteristics and baseline respiratory health of the host.

This issue of *European Respiratory Monograph* (*ERM*) covers the spectrum of bronchial infection, from the milder to the most severe. After explaining the mechanisms of defence within the bronchial tree, the different chapters will elegantly show the clinical manifestations, treatment and prognosis of these frequent diseases.

A number of chapters are dedicated to the chronic bronchial infection in COPD. Up to 10% of adults over the age of 40 years are affected by COPD. The impaired host defences in COPD allow the establishment and proliferation of potentially pathogenic microorganisms (PPMs). Repeated isolation of PPMs in bronchial secretions in stable patients was defined as colonisation; however, it is well documented that the presence of PPMs in the lower airways is associated with increased exacerbation frequency and severity, a faster lung function decline and worse health status. Therefore, the term chronic bronchial infection (CBI) has been proposed to define this clinical situation. The presence of CBI in COPD is characterised by increased chronic inflammation not only in the airways and lung parenchyma, but also at a systemic level. Current evidence indicates that a significant amount of local and systemic inflammatory response in COPD may be attributable to the presence of PPMs. Since atherosclerosis is also characterised by chronic inflammation and oxidative stress, it has been hypothesised that CBI may be responsible for some extrapulmonary manifestations of COPD, particularly the high prevalence of cardiovascular comorbidities.

CBI is linked to acute episodes of increased symptoms, the so-called exacerbations of COPD, which is also covered in this current issue of the *ERM*, from the point of view of: the different infective aetiologies; viruses and bacteria and their interrelationships; the impact of exacerbations

Eur Respir Monogr 2013; 60: ix–x. Copyright ERS 2013. DOI: 10.1183/1025448x.10005313. Print ISBN: 978-1-84984-034-7. Online ISBN: 978-1-84984-035-4. Print ISSN: 1025-448x. Online ISSN: 2075-6674.

in the course of the disease; antimicrobial treatment and prevention; and along with new evidence for the use of long-term antibiotics in a selected group of patients with COPD and frequent exacerbations.

Finally, there are a number of chapters dedicated to bronchiectasis, once considered an orphan lung disease. In contrast, there is an increased interest in the aetiology, natural history and treatment of bronchiectasis, either as an isolated disease or as a complication of another respiratory condition, such as COPD. The innovative administration of antibiotics by inhalation may represent an advance in the treatment of CBI in bronchiectasis, and the development of new formulations of old antibiotics to be administered by this route will provide a new therapeutic option for some of the most difficult-to-treat severe patients with bronchial infections.

We are sure that clinicians will find this *ERM*'s summary of the existing evidence within this field, alongside some of the most relevant and new information that has arisen to date, as a great aid to them in improving their practice and care for patients with these very frequent respiratory problems.

Chapter 1

Acute bronchitis: aetiology and treatment

Carl Llor

SUMMARY: Acute bronchitis is an inflammation of the tracheobronchial tree that occurs most commonly during the winter months and is associated with respiratory viruses. The role of bacteria in this infection is controversial, as bronchial biopsies have never demonstrated bacterial invasion. Treatment is generally symptomatic, directed at the relief of troublesome respiratory symptoms, particularly cough. Most of these lower respiratory tract infections are self-limiting and several studies suggest that antimicrobial treatment does not significantly shorten the duration of cough. However, many patients are prescribed antibiotics, mainly when discoloured sputum is present. Approaches to controlling acute cough have included narcotic cough suppressants, expectorants, mucolytics, antihistamines, decongestants, β_2-agonists, analgesics, nonsteroidal anti-inflammatory drugs and herbal remedies. Despite the fact that these drugs are widely prescribed, there is little evidence that their routine use is helpful for adults with cough. However, guidelines suggest that a short trial of an antitussive medication, mainly dextromethorphan, may be reasonable, as well as β_2-agonists in adults with bronchial obstruction.

KEYWORDS: Acute bronchitis, acute cough, respiratory inflammation, treatment

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Eur Respir Monogr 2013; 60: 1–17.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10016912
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Acute bronchitis is a clinical term that implies a self-limiting infection of the large airways and is characterised by clinical manifestations of cough without pneumonia with, or preceded by, other symptoms of upper respiratory tract infection. Clinical features of acute bronchitis include cough, sputum production, wheeze and symptoms of an associated upper respiratory tract infection, including headache, myalgias and malaise [1]. Fever may be present in some patients with acute bronchitis; however, prolonged or high-grade fever should prompt consideration of pneumonia or influenza. After several days of coughing, chest wall or abdominal discomfort that is muscular in nature may be noted. The cough, which constitutes the most prominent manifestation of acute bronchitis, lasts for less than 3 weeks in 50% of patients, but for more than 1 month in 25% of patients [2]. Initially, the cough is nonproductive but later, mucoid sputum is produced. Still later in the course of the illness, purulent sputum is present. Many patients with acute bronchitis also have tracheitis. Physical findings are generally nonspecific and the chest radiograph is normal.

It is a very prevalent disease and is one of the most frequent causes of medical visits in primary care [3, 4]. About 5% of adults self-report an episode of acute bronchitis each year with a higher incidence observed during the winter and autumn [5, 6]. Despite being a self-limiting condition, most patients feel ill and many do not perform their usual activities. Patients often return to their physician or seek other medical help because the symptoms may persist, mainly cough, which may be very bothersome for some [7]. Furthermore, patients with bronchitis miss an average of 2–3 days of work per episode [8].

Recurrent attacks of acute bronchitis in a previously healthy person are unusual and other conditions, particularly asthma, must be ruled out. Suspicion and work-up for asthma should be reserved for patients with cough lasting longer than 3 weeks [3].

Aetiology

Acute bronchitis consists of an inflammation of the large airways of the epithelium of the bronchi, usually caused by infection. Microscopic examination demonstrates a thickening of the bronchial and tracheal mucosa corresponding to the inflamed areas. These pathological findings are consistent with reports of proximal lower airway inflammation observed by positron emission tomography [9]. As many as 41% of patients present with significant reductions in forced respiratory volume in 1 s (FEV_1), with values of less than 80% predicted, or bronchial hyperreactivity, with improvement during the following 5–6 weeks [10]. In a Dutch study, THIADENS *et al.* [11] observed that 39% of otherwise healthy subjects coughing for a period of at least 2 weeks attending a general practitioner showed features of asthma and an additional 7% were diagnosed with chronic obstructive pulmonary disease (COPD).

In the majority of studies of acute bronchitis, there is a large proportion of cases with no pathogen identified, either because the appropriate tests were not performed (as is usually the rule in outpatients) or the organism was missed. However, viral aetiology is thought to be the cause of approximately 90% of the cases [12, 13]. Influenza A and B viruses are the most common pathogens isolated in patients with uncomplicated acute bronchitis. This cause is associated with an abrupt onset with fever, chills, headache, muscle aches and tracheobronchitis. Epidemiological peaks are common. Another frequent aetiology is parainfluenza virus, with outbreaks occurring more commonly in autumn and in nursing homes. The presence of croup in a child is very suggestive of parainfluenza virus infection. Respiratory syncytial virus (RSV) is common in children less than 1 year of age and in elderly patients in nursing homes, with outbreaks occurring in winter or spring. Family history is important in these cases. Human metapneumovirus has also been identified as a causative agent [12–14]. A French study involving adults who had been vaccinated against influenza showed a viral cause in 37% of 164 cases of acute bronchitis, of which 21% were rhinovirus [15]. Both rhinovirus and enterovirus generally cause a mild infection. Other aetiologies are coronavirus, which causes severe respiratory symptoms in elderly patients and adenovirus that causes an infection clinically similar to influenza. Multiple viral infections are detected in 30% of the episodes of acute bronchitis [16].

The role of bacteria in this infection continues to be controversial [1]. Bacterial species commonly implicated in community-acquired pneumonias are isolated from the sputum in a minority of patients with acute bronchitis [1]. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* have been isolated from sputum samples in up to 45% of patients with acute bronchitis [17, 18], but their role is difficult to assess because of potential oropharyngeal colonisation in healthy individuals [19, 20]. Furthermore, bronchial biopsies have not shown bacterial invasion. Atypical bacteria are important causes of acute bronchitis, including *Mycoplasma pneumoniae*, *Bordetella pertussis* and *Chlamydophila pneumoniae* [17, 21–32]. *M. pneumoniae* infection presents an incubation period of 2–3 weeks with symptoms initiating gradually, in 2–3 days. It has been identified in clusters among college students and military recruits. *C. pneumoniae* infection, with an incubation period of 3 weeks, presents gradually with hoarseness before cough. Clusters of infection have also been reported among military recruits,

college students and patients in nursing homes. *B. pertussis* has an incubation period of 1–3 weeks and affects mainly adolescents and young adults. Whooping only occurs in a minority of patients. Fever is also uncommon but marked leukocytosis with lymphocytic predominance can occur. The prevalence of pertussis has decreased recently because of vaccination campaigns [33]. However, some studies have shown that the prevalence of pertussis has slightly increased again over the last decade, accounting for 1–6% of cases of acute bronchitis [34–38].

Treatment

Acute bronchitis is often managed in the community by general practitioners. The treatment is typically broken down into two categories: symptom management and antimicrobial therapy. However, physicians very often appear to deviate from evidence-based medical practice in the treatment of bronchitis, as neither treatment is effective and, in some cases, their benefit is only marginal (table 1).

This chapter focuses on uncomplicated acute bronchitis, as opposed to acute bronchitis in patients with underlying lung or heart disease or immunosuppression. Acute bronchitis in patients with documented emphysema or chronic bronchitis, for example, is usually considered a distinct clinical entity (acute exacerbation of chronic bronchitis). Because patients with significant comorbidities, particularly congestive heart failure and immunosuppression, have been routinely excluded from treatment studies of acute bronchitis, the generalisability of the findings to patients with these comorbid conditions is unknown.

Symptom management

Treatment of patients with acute bronchitis is generally symptomatic, directed at relief of troublesome respiratory symptoms, particularly cough and wheezing. Common therapies include cough suppressants, expectorants, mucolytics, antihistamines, decongestants, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), β_2-agonists and alternative therapies. Most of these therapies are available as over-the-counter medicines in most countries and can be obtained in pharmacies, chemists and shops without medical prescription, as opposed to prescription-only medicines. A US telephone survey of medication use indicated that in a given week, approximately 10% of children are given an over-the-counter preparation by their parents for their cough [39].

Table 1. Clinical recommendations for acute bronchitis and evidence rating

Recommendation	Evidence rating
Increased fluid intake, heated and humidified air, and avoidance of smoking and second-hand tobacco smoke	C
Antibiotics should not be routinely used	A
Antivirals should not be routinely used	B
Antitussives (dextromethorphan, codeine and hydrocodone) are recommended in adults	B
Antitussives are not recommended in children	C
β_2-agonist inhalers are recommended in patients with wheezing	B
β_2-agonist inhalers are not recommended in patients without wheezing	B
Expectorants are not recommended in adults	B
High-dose episodic inhaled corticosteroids are recommended	B
Analgesics and NSAIDs are recommended	B
Echinacea is recommended	B
Pelargonium is recommended	B
Chinese herbs are recommended	B
Honey is recommended in children	B

NSAID: nonsteroidal anti-inflammatory drug; A: consistent, good-quality evidence; B: inconsistent or limited-quality evidence; C: consensus, disease-oriented evidence, usual practice, expert opinion or case series. Reproduced and modified from [2] with permission from the publisher.

However, there is little evidence that the routine use of these drugs is helpful for patients with acute cough. Some studies did report some slight beneficial effects from some of these drugs, but these studies were small and had methodological flaws [40, 41].

Although evidence from randomised, controlled trials is lacking, low-cost and low-risk actions, such as elimination of environmental cough triggers (*e.g.* dust) and vaporised air treatments, particularly in environments with low humidity, are reasonable treatment options, mainly if symptoms of nasal congestion and runny nose are present. Treatment should include good hand hygiene, increased fluid intake, and avoidance of smoking and second-hand tobacco smoke.

Antitussives

Although they are commonly used and suggested by physicians, antitussives are not recommended for routine use in patients with bronchitis [40]. Cough preparations may contain different drugs with a variety of modes of action, which can make them difficult to compare [42]. Among studies in adults, six clinical trials including 1526 patients compared antitussives with placebo, with conflicting results. Most of these studies, however, were carried out in patients with acute cough in the context of an upper respiratory tract infection, limiting the external validity of these studies to patients with acute bronchitis. Dextromethorphan was examined in three of these trials [43–45]. One of these studies favoured this cough suppressant, at a dose of 30 mg given in a single dose, over placebo in terms of cough counts and subjective visual analogue scales [43]. The other two studies showed marginal superiority of the drug compared to placebo [44, 45]. No double-blind placebo-controlled study has evaluated the use of codeine on cough with acute bronchitis but in the two studies published, this drug appeared to be no more effective than placebo in reducing cough symptoms [46, 47]. In fact, one of these studies tested codeine at a dose of 30 mg four times daily for 4 days and the drug was no more effective than placebo either as a single dose or in a total daily dose of 120 mg [46].

In studies in children, antitussives (two studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo. Particularly, some studies have shown that dextromethorphan is ineffective for cough suppression in children with bronchitis [48]. One trial tested two paediatric cough syrups and both preparations showed satisfactory response in 46% and 56% of children, respectively, compared to 21% of children in the placebo group [40]. These data, coupled with the risk of adverse events in children, including sedation and death, prompted the American Academy of Pediatrics and the US Food and Drug Administration (FDA) to recommend against the use of antitussive medications in children younger than 2 years [49]. The FDA subsequently recommended that cough and cold preparations not be used in children younger than 6 years. Use of adult preparations in children and dosing without appropriate measuring devices are two common sources of risk to young children [50]. Some guidelines recommend a short course of antitussives, such as hydrocodone, codeine or dextromethorphan, to reduce severe coughing during acute illness in adults and children older than 6 years, given their benefit in patients with chronic bronchitis [51]. Antitussive therapy might be given to those patients with a cough causing discomfort where inhibition of airway secretion clearance will not delay healing. According to evidence published to date, in cases in which a cough-suppressant agent is administered, dextromethorphan can be recommended in adults. However, the tendency of these agents to dry bronchial secretions may aggravate the cough and prolong recovery.

Expectorants and mucolytics

Expectorants may be indicated in patients requiring clearance of airway secretions. Physicians commonly prescribe guaifenesin in doses of 600 to 1200 mg and it is a component in many over-the-counter antitussive therapies. Two trials including only 304 participants compared guaifenesin with placebo [40, 52, 53]; one indicated significant benefit whereas the other did not [40]. In fact, in the positive study, 75% of participants taking this expectorant for acute cough stated that it was helpful in terms of reducing cough frequency and intensity compared to 31% in the control group on the third day [53]. The clinical effectiveness of this type of therapy is, however, questionable, and therapeutic trials have failed to show favourable effects on the cough associated with acute bronchitis [40].

Two trials have been carried out with mucolytics (letosteine in children and bromhexine in adults) in patients with acute cough and the results showed a marginal benefit of both drugs compared to placebo [54, 55].

Decongestants and antihistamines

Antihistamines have been included in cough remedies for decades. Two studies examined antihistamine–decongestant combinations in adults with common cold but not acute bronchitis [40]. These studies compared loratadine and dexbrompheniramine with pseudoephedrine, showing conflicting results. Two other studies involving only children compared combinations of antihistamines and decongestants for the common cold but the drugs did not appear to be more effective than placebo [40]. Four studies compared other combinations of drugs with placebo and indicated some benefit in reducing cough symptoms. Three trials involving 1900 adults compared antihistamines, mainly terfenadine, with placebo but they failed to show a benefit in relieving cough symptoms [40]. Similarly, these studies only included patients with the common cold. Two studies comparing antihistamines with placebo were carried out in children with acute cough. One of these studies showed that clemastine was not more effective than placebo. The other trial included an arm with diphenhydramine taken in a single nocturnal dose; diphenhydramine was no more effective than dextromethorphan or placebo in reducing cough frequency or impact on child or parental sleep [56]. Physicians should be aware of these results, since diphenhydramine is widely used and these studies indicated limited clinical effectiveness [57].

Analgesics and NSAIDs

No randomised clinical trials on the effects of analgesics in people with acute bronchitis have been performed. Notwithstanding, both analgesics and NSAIDs are widely prescribed in patients with lower respiratory tract infections, mainly for alleviating fever, headache, myalgias and chest pain, as well as other common complaints, such as cough [58]. Evidence of the effectiveness of NSAIDs in this acute respiratory tract infection is lacking. Two clinical trials comparing NSAIDs and antibiotics in acute bronchitis were published some time ago. In a small clinical trial carried out in Italy, GIRBINO *et al.* [59] demonstrated a more rapid regression of bronchial inflammation in the subjects treated with amoxicillin (one 1-g tablet twice a day) and a NSAID (one 700-mg tablet of morniflumate twice a day) compared to those treated only with the antibiotic. One new randomised clinical trial on the effects of an inhaled anti-inflammatory drug, fluticasone, in patients with acute cough showed a small effect on symptom severity in the second week of disease. The clinical relevance of this effect is, however, doubtful [60]. In another double-blind, placebo-controlled trial carried out in 45 hospitalised adult patients requiring antibiotic therapy for acute or chronic respiratory tract infections, those assigned to antibiotic treatment with the concomitant use of nimesulide (100 mg twice daily) over a period of 15 to 23 days had a greater and more rapid improvement in the signs and symptoms of respiratory tract infection, such as chest pain and cough, than those treated with antibiotic plus placebo [61]. Because of the small size of these studies we cannot recommend the use of these drugs in clinical practice.

Bronchodilators

The rationale for using bronchodilators in patients with acute bronchitis is supported by the fact that cough is the primary symptom in some patients suffering from asthma and most of such people may have resolution of symptoms with β_2-agonist drugs [62]. In addition, when infected with atypical and viral pathogens known to cause acute bronchitis, patients usually have impaired airflow from bronchial reactivity [63]. Despite these facts, the few randomised, placebo-controlled trials carried out, which have involved small numbers of patients, do not support the routine use of β_2-agonist inhalers in patients with acute bronchitis [41]. Five randomised, controlled trials have examined the efficacy of these drugs [64–68]. The effect of albuterol (salbutamol), specifically either oral or inhaled, on cough has been studied in four randomised trials [64–67]. LITTENBERG *et al.* [64] conducted a study in 104 adults with cough of less than 4 weeks' duration comparing albuterol 4 mg orally thrice daily for 7 days with placebo. The study found no significant differences between patients receiving albuterol as compared to placebo in measures of efficacy,

with significantly more adverse effects being observed in the treatment group. HUESTON [65] investigated the efficacy of albuterol compared to erythromycin, both given as liquid preparations, in adults presenting with cough. There were fewer patients in the albuterol group with productive cough at 7 days compared to the erythromycin group, but there was no difference in missed days of work or daily activities. The study was repeated using an albuterol inhaler with similar findings of reduced cough at 7 days [66]. In the study by TUKIANEN *et al.* [67], the mean severity of night cough was less in the albuterol plus dextromethorphan group than in the dextromethorphan alone group on days 3 and 4 but there were no differences in the severity or frequency of day cough, ease of expectoration or sputum production on any day. A study by MELBYE *et al.* [68] compared inhaled fenoterol with placebo in 80 patients with acute bronchitis. An improvement was observed in symptom scores on day 2 for those patients receiving fenoterol presenting with bronchial hyperresponsiveness, wheezes on auscultation or a FEV_1 less than 80% compared to the same patient group receiving placebo. Patients with normal lung findings at the start of the study did not improve with treatment. Two trials in children with no evidence of airway obstruction did not show any benefits from the use of oral β_2-agonists [69, 70].

Patients presenting with acute bronchitis may have bronchospasm and treatment with a bronchodilator would, therefore, be effective. Studies have shown a slight decrease in cough and have observed patients returning to work earlier when treated with bronchodilators compared with those treated with antibiotic therapy [65, 66]. There are consistent data to support the use of β_2-agonist therapy in decreasing the duration of cough in patients with bothersome cough and airway hyperresponsiveness [64–68]. However, a recent Cochrane Review of five trials involving 418 adults showed that even among patients with airflow obstruction, the potential benefit of β_2-agonists is not well supported [41]. Adults given β_2-agonists were more likely to report tremor, shakiness or nervousness, with a risk ratio (RR) of 7.94 (95% CI 1.2–53.9, number needed to treat to harm 2.3). In conclusion, if a patient has airway hyperresponsiveness, a β_2-agonist might be given but must be weighed against the adverse effects of these medications and this treatment should be withheld in patients without wheezing [41].

Regarding other bronchodilators, whether anticholinergic bronchodilator treatment is effective in patients with acute bronchitis is not known. A Cochrane Review suggests that there may be some benefit with high-dose, episodic inhaled corticosteroids, but no benefit occurs with low-dose, preventive therapy [71]. There are no data to support the use of oral corticosteroids in patients with acute bronchitis and no asthma.

Herbal remedies

Many patients also use over-the-counter alternative medications for relief of their bronchitis symptoms. Studies have assessed the benefits of echinacea, pelargonium and Chinese herbs. Trials of echinacea in patients with bronchitis have yielded inconsistent results, and positive results have been modest at best [72]. Several randomised trials have evaluated pelargonium as a therapy for bronchitis [73–75]. Modest benefits have been noted, primarily in symptom scoring by patients [74]. In one randomised trial, patients taking pelargonium for bronchitis returned to work an average of 2 days earlier than those taking placebo [75]. A Cochrane Review including three trials involving 746 patients highlights the substantial heterogeneity for all relevant outcomes and three other trials including 819 children were similarly inconsistent for acute bronchitis in children [73]. Some concerns about possible hepatotoxicity of this plant have been suggested even though a recent analysis discarded a causative relationship [76].

Chinese herbs are considered to have antiviral, antitussive, antiasthmatic and fever-relieving properties. However, trials comparing these medicinal herbs with placebo for the treatment of uncomplicated acute bronchitis, which included 74 studies of insufficient quality involving 6877 participants, do not recommend the routine use of these herbs [77]. In addition, the safety of Chinese herbs is unknown due to the lack of toxicological evidence for these herbs, although adverse events were reported in some case reports [77].

Other alternative therapies

One recent Cochrane Review examined the effectiveness of honey for acute bronchitis in children [78]. The authors included two randomised clinical trials with 265 children comparing the effect of honey with dextromethorphan, diphenhydramine and no treatment on symptomatic relief of cough [79, 80]. Honey was better than either no treatment or the antihistamine drug in reducing the frequency of cough but did not differ significantly from the antitussive in reducing cough frequency. Adverse events included mild reactions such as nervousness, insomnia and hyperreactivity in nearly 10% of the children included. Although the authors of these studies concluded that symptom scores from patients treated with honey were superior to those treated with placebo, the clinical benefit was small [78].

Antimicrobials

Most systematic reviews have found no benefit from the use of antimicrobials with the exception of a modest reduction in the duration of symptoms [81]. A recent meta-analysis, including 15 clinical trials with 2618 patients examining the effects of antibiotics (erythromycin, azithromycin, amoxicillin, amoxicillin/clavulanate, doxycycline, trimethoprim-sulfamethoxazole and cefuroxime) did have better outcomes than those receiving placebo in patients with acute bronchitis [23, 65, 82–95]. At follow-up, patients receiving antibiotics were marginally more likely to show clinical improvement than those receiving placebo treatment (nine studies with 1754 patients; RR 1.06, 95% CI 1.0–1.1) [82]. In fact, patients given antibiotics were less likely to have cough (four studies with 275 participants; RR 0.64, 95% CI 0.5–0.9; number needed to treat for an additional beneficial outcome (NNTB) 6), night cough (four studies with 538 participants; RR 0.67, 95% CI 0.5–0.8; NNTB 7), no improvement according to the clinician's global assessment (six studies with 891 participants; RR 0.61, 95% CI 0.5–0.8; NNTB 25) and an abnormal lung examination (five studies with 613 participants; RR 0.54, 95% CI 0.4–0.7; NNTB 6). Patients receiving antibiotics also had a reduction in days feeling ill (five studies with 809 participants; mean difference 0.64 days, 95% CI 1.2–0.1 days). The differences in the presence of a productive cough at follow-up, proportions with activity limitations at follow-up, mean duration of cough and mean duration of productive cough did not reach statistical significance. All these results, despite being beneficial for antibiotics, may have overestimated the benefits of antibiotics, as the authors of this meta-analysis were unable to include data from the study published by Stott and West [94] for the outcomes of cough and night cough at follow-up, which were reported in the published trial as being not significantly different between the group treated with antibiotics and the control group.

The authors of this meta-analysis also stated that it is possible that the overall benefit noted from antibiotics resulted from the inclusion of patients who may have had pneumonia instead of acute bronchitis in some trials, because only one trial obtained chest radiographs in all patients [83] and then excluded those whose radiographs were consistent with pneumonia. All other studies either excluded or obtained chest radiographs in patients with only clinical findings of suspected pneumonia [82]. However, since the prevalence of pneumonia in outpatients who present with acute cough is generally low, approximately 5% on the basis of a recent paper published with the data of the GRACE (Genomics to Combat Resistance Against Antibiotics in Community Acquired Lower Respiratory Tract Infections in Europe) study [96], it is unlikely that a significant number of patients in the trials included in this meta-analysis had pneumonia.

Another randomised clinical trial, based on the data of GRACE study, not included in the Cochrane Review, has recently been published [97]. It constitutes, by far, the largest study carried out, including 16 networks in 12 different European countries with 2061 patients aged 18 years or older with acute cough of less than 1 month duration as the prominent symptom and once pneumonia was excluded on the basis of clinical grounds. Patients were assigned to either amoxicillin 1 g or placebo taken thrice daily. Symptoms rated moderately bad or worse, which was considered the main outcome, lasted a median of 6 days in the antibiotic group and 7 days in the placebo group, with the difference not being significant (hazard ratio (HR) 1.06, 95% CI 0.96–1.18). Curiously, the exclusion of patients with asthma or COPD made little difference to the

estimates of duration of symptoms rated moderately bad or worse (HR 1.04), nor were differences observed when the authors only considered patients aged 60 years or older (HR 0.95, 95% CI 0.79–1.14). The secondary outcomes considered in this trial were not statistically significant, as symptom severity at days 2–4 after the index consultation was 1.69 with placebo and 1.62 with antibiotics, with a difference of -0.07 (95% CI -0.15–0.007). However, the number of new or worsening symptoms was significantly less common in the amoxicillin than in the placebo group (15.9% *versus* 19.3%), with a number needed to treat of 30.

The percentage of adverse events was higher in the groups assigned to antibiotic therapy in all these reviews. One meta-analysis showed a number needed to harm (based on antibiotic adverse effects) of 16.7 [98]. In the study by LITTLE *et al.* [97], adverse events were also significantly more common in the antibiotic group, with a number needed to harm of 21 (95% CI 11–174). The most commonly reported side-effects involved gastrointestinal symptoms such as nausea, vomiting or diarrhoea.

Current guidelines, endorsed by a number of national societies, including the European Respiratory Society and Infectious Diseases Society of America, and the UK National Institute for Health and Clinical Excellence, do not recommend the routine use of antibiotics for uncomplicated acute bronchitis in otherwise normal persons [3, 99, 100]. Nonetheless, after their introduction in the 1940s, antibacterial agents were rapidly embraced for treatment of acute bronchitis. Arguments against using antibiotics in acute bronchitis include the costs, the presence of potential adverse effects, the containment of antimicrobial resistance and the promotion of self-care [101, 102]. Because of the risk of antibiotic resistance and of *Clostridium difficile* infection in the community, antibiotics should not be routinely used in the treatment of acute bronchitis, especially in younger patients in whom pertussis is not suspected.

Although 90% of bronchitis infections are caused by viruses, approximately two-thirds of patients in Western countries are treated with antibiotics. Patient expectations may lead to antibiotic prescription. A survey showed that 55% of patients believed that antibiotics were effective for the treatment of viral upper respiratory tract infections and that nearly 25% of patients had self-treated an upper respiratory tract illness in the previous year with antibiotics left over from earlier infections. Studies have shown that the duration of office visits for acute respiratory infection is unchanged or only 1 min longer when antibiotics are not prescribed [103, 104]. At present, more than 60% of patients receive antimicrobials for this diagnosis and it is currently one of the five most frequently cited infections for excessive antibiotic use in outpatients [105–112]. In a recent study carried out in the primary care setting in the USA, 91% of the patients diagnosed with acute bronchitis were treated with antibiotics [113]. Many physicians may not give antibiotics on the first visit but are more likely to prescribe these antibacterials on subsequent visits, mainly if discoloured sputum is associated. In a prospective study of more than 3000 adults with acute cough due a lower respiratory tract infection in 13 European countries, BUTLER *et al.* [114] observed that patients who presented with purulent sputum were prescribed antibiotics 3.2 times more frequently (95% CI 2.1–5.0) than those without sputum but that antibiotic treatment was of no benefit in terms of symptomatic improvement, regardless of sputum colour. COENEN *et al.* [115] observed that the presence of sputum was associated with an increased risk of antibiotic prescription independent of patient and clinician characteristics (OR 2.5, 95% CI 1.6–3.9). FISCHER *et al.* [116] directly observed 30 primary care physicians in Germany managing 237 patients with respiratory tract infections and found that purulent sputum was associated with an increased chance of antibiotic prescription (OR 2.1, 95% CI 1.1–4.1). In another study from Germany, HUMMERS-PRADIER *et al.* [117] found increased antibiotic prescription for respiratory tract infections when patients had yellow or green sputum (OR 4.4, 95% CI 1.8–10.7). In the Netherlands, discoloured sputum was related to antibiotic treatment and was one of the reasons for overprescribing in lower respiratory infections [118]. In the USA, GONZALES *et al.* [119] found antibiotic prescription for upper respiratory tract infections was increased when patients produced green sputum (OR 4.8, 95% CI 2.4–11.1) and DOSH *et al.* [120] found antibiotic prescription was increased in association with smokers coughing up green or yellow sputum (OR 2.5, 95% CI 1.7–3.8).

This aspect is even more important as more than half of patients with acute bronchitis report the production of purulent expectoration [121]. Peroxidase released by the leukocytes in sputum causes the colour changes; hence, colour alone should not be considered indicative of bacterial infection [122]. ALTINER *et al.* [123] obtained sputum samples from 241 patients with acute cough in primary care and found 136 of these were coloured yellow or greenish. Only 28 samples yielded pathogens on culture. The sensitivity of yellowish or greenish sputum as a test for bacterial infection was 0.79 (95% CI 0.6–0.9) and the specificity 0.46 (95% CI 0.04–0.5). Another explanation for the frequent prescription of antibiotics is the lack of distinction between acute and chronic bronchitis. This fact may explain why clinicians perceive antibiotics to be more beneficial to smokers [124].

Identifying the subgroup that will probably benefit from antibiotic use is difficult; it is most important to rule out the presence of pneumonia when considering treatment [105]. Patients with symptoms of upper respiratory illness and those who have been sick for less than a week may be the least likely to benefit from therapy with an antibiotic [82].

When can antimicrobial therapy be considered? Although antimicrobials are not recommended for routine use in patients with bronchitis, they may be considered in certain situations. First, antimicrobial agents should be prescribed for patients with acute bronchitis who are very unwell. Second, antimicrobials should also be considered for patients older than 65 years who also have serious comorbidities such as heart failure, insulin-dependent diabetes mellitus and/or a serious neurological disorder [3]. Third, antimicrobial therapy may be more beneficial when a treatable pathogen is suspected. For instance, when pertussis is suspected as the aetiology of cough, initiation of a macrolide antibiotic is recommended to limit transmission, even though there is no evidence supporting this. With the possible exception of therapy initiated during the first week of symptoms, there are no compelling data to support the prospect that cough will be less severe or shorter in duration with antibiotic therapy [125]. On the basis of a recent review by the Cochrane Library including 11 clinical trials with 1796 patients, the best regimen for microbiological clearance, with fewer side-effects, is a 3-day course of azithromycin 10 $mg \cdot kg^{-1}$ per day [125].

An argument for the use of antibiotics in acute bronchitis is that it may decrease the risk of subsequent pneumonia. A large cohort study within the UK General Practice Research Database indicated that the risk of pneumonia as a complication of lower respiratory tract infection was substantially reduced in patients aged 65 years or older when antibiotics had been prescribed immediately [112]. The number needed to treat to prevent one case of pneumonia in the month following an episode of acute bronchitis was 119 in patients 16–64 years of age, but only of 39 in elderly patients. However, sicker patients and those more likely to have complications would have been more likely to be offered immediate antibiotics [126]. The results of this study are in sharp contrast to those of the largest multicentre randomised placebo-controlled study of antibiotics for uncomplicated lower respiratory tract infections published up to now, as LITTLE *et al.* [97] failed to observe relevant effects of antimicrobial therapy in elderly patients with lower respiratory tract infections. In the 226 participants aged 70 years or older, the differences between treatment groups for symptom severity and symptom duration were not significant [97]. The limited benefits of antibiotics need to be considered in the context of the potential side-effects, medicalisation of a self-limiting condition and costs of antibiotic use, such as increasing resistance of organisms to antibiotics. However, antimicrobials should be considered in suspected cases of pneumonia or in selected cases of acute exacerbations in patients with underlying COPD, since the efficacy of antibiotics is well established in purulent exacerbations of severe COPD [127] and in purulent ambulatory exacerbations of mild-to-moderate COPD in primary care [128].

Neuraminidase inhibitors could be considered during influenza season for high-risk patients who present within 24 h of symptom onset, as they decrease the duration of symptoms by approximately 21 h [129]. JEFFERSON *et al.* [130] have published a Cochrane Review including and analysing data from 25 studies (15 oseltamivir and 10 zanamivir studies) but they failed to use data from a further 42 studies due to insufficient information or unresolved discrepancies in their data. They found it difficult to draw hard conclusions regarding the other effects of neuraminidase

inhibitors on the efficacy outcomes of key importance to this review, such as viral transmission and complications of influenza, and there was no evidence of an effect on hospitalisations [130]. Furthermore, two unpublished studies have found no statistically significant reduction in the duration of symptoms in elderly and chronically ill patients [131]. In addition, antiviral medication is often inappropriately prescribed, usually starting beyond day 1 of symptom onset [132]. This high risk of publication and reporting biases limits the widespread use of these antivirals for the treatment of influenza virus infections and, therefore, the empirical use of this treatment in low-risk patients suspected of having influenza should not be recommended.

Reducing unnecessary antibiotic prescribing

Many patients with acute bronchitis expect medications for symptom relief and physicians are faced with the difficult task of convincing patients that an effective treatment against this infection is lacking. Table 2 includes some hints that may facilitate these discussions. In a Cochrane Review on interventions to improve antibiotic prescribing practices in primary care including a total of 39 studies, multifaceted interventions combining physician, patient and public education in a variety of venues and formats were the most successful in reducing antibiotic prescribing for inappropriate indications, with interactive educational meetings being more effective than didactic lectures [133]. In a paper published recently, VAN DER VELDEN *et al.* [134] assessed the effectiveness of physician-targeted interventions aiming to improve antibiotic prescribing for respiratory tract infections in primary care. The authors included a total of 58 studies observing that overall antibiotic prescription was reduced by 11.6%. Within the 59 interventions aiming to decrease overall prescription, multiple interventions were more frequently effective than interventions using one element and multifaceted interventions containing at least educational materials for physicians were the most effective strategies. The authors observed that communication skills training and near-patient testing achieved the largest intervention effects [134].

CALS and co-workers [135, 136] showed dramatic decreases in antibiotic prescriptions when general practitioners used C-reactive protein (CRP) testing to guide antibiotic management in lower respiratory tract infections, observing reductions from 53% to 31% in one of the studies and from 56.6% to 43.4% in the other. Furthermore, no differences in clinical outcomes were observed between patients treated and not treated with antibiotics. The major contribution of point-of-care CRP testing seems to be in decreasing uncertainty, adding useful information that helps to identify those patients not at risk for a complicated illness course. In fact, distinguishing pneumonia from acute bronchitis with only clinical findings is problematic in primary care, and rapid CRP testing has been shown to perform better in predicting the diagnosis of pneumonia than any individual or combination of clinical symptoms and signs in lower respiratory tract infection [137, 138], and may thereby help identify those patients who will benefit from antibiotic treatment.

The IMPAC3T (Improving Management of Patients with Acute Cough by C-reactive Protein Point of Care Testing and Communication Training) study tested two interventions (use of rapid CRP testing and enhanced communication skills) in a factorial design and demonstrated that intensive training for general practitioners in enhanced communication skills, using repeated

Table 2. Communication tips that can help with patients with acute bronchitis

Discuss with the patient that no treatment has shown to be clearly effective for reducing the symptoms of acute bronchitis
Set realistic expectations for symptom duration, mainly for cough (about 3 weeks)
Define the diagnosis as a chest cold or viral respiratory infection instead of using the term acute bronchitis
Explain that antibiotics do not significantly reduce the duration of symptoms, and that they may cause adverse effects and lead to antibiotic resistance
Consider delayed prescription of antibiotics
Consider use of rapid tests, such as rapid C-reactive protein testing, and discuss the results with the patient

consultations with simulated patients and personal feedback, provided a 20% reduction in antibiotic prescribing for lower respiratory tract infections [135]. The STAR (Stemming the Tide of Antibiotic Resistance) programme of five sessions of web-based training in enhanced communication skills, with patient scenarios and an expert-led, face-to-face seminar, achieved a 4.2% (95% CI 0.6–7.7%) reduction in global antibiotic use with no significant changes in admissions to hospital, reconsultations or costs [139]. FRANCIS *et al.* [140] showed that the use of a brief web-based training programme and an interactive booklet on respiratory tract infections in children with uncomplicated respiratory tract infections within primary care consultations led to an important reduction in antibiotic prescribing, with an odds ratio of 0.29 (95% CI 0.14–0.60), and reduced intention to consult without reducing satisfaction with care.

GONZALES *et al.* [141] conducted a three-group randomised study at 33 primary care practices in the USA evaluating the effectiveness of two interventions. In one-third of the practices, the intervention was printed decision support in which educational brochures were given by triage nurses to patients with cough illnesses as part of routine care, and in another third of the practices a computer-assisted decision support intervention was implemented so that when triage nurses entered ''cough'' into the electronic health record, an alert would prompt the nurse to provide an educational brochure to the patient; the remaining practices were control sites. Compared with the baseline period, the percentage of subjects prescribed antibiotics for uncomplicated acute bronchitis during the intervention period decreased from 80% to 68.3% at the printed decision support intervention sites and from 74% to 60.7% at the computer-assisted decision support intervention sites [141].

Communicating the possible length of mainly bothersome coughs is important in acute bronchitis, since the mean duration of any cough is 17.8 days. In a recent study, EBELL *et al.* [142] performed a population-based survey in the USA to determine expectations regarding the duration of acute cough, reporting a median duration of 5 to 7 days. The mismatch between patients' expectations and reality for the natural history of acute cough illness has important implications for antibiotic prescribing. If a patient expects that an episode of acute cough should last about 1 week, it makes sense that they might seek care for that episode and request an antibiotic after 5 or 6 days. Notwithstanding, general practitioners often fail to satisfactorily communicate the mean length of cough to patients with acute bronchitis [143]. As physicians, we must avoid sentences like ''With the pills I am prescribing, you will feel a rapid remission of your cough'', as if the cough does not remit within the time expectation of the patient, they will be prone to consult again and will probably demand drugs that are perceived as stronger, such as antibiotics. Educating patients about the natural history of bronchitis is therefore crucial. Patients need to know that antibiotics are probably not going to be beneficial and that treatment with antibiotics is associated with significant risks and side-effects. They should also be told that it is normal to still be coughing 2 or even 3 weeks after onset, and that they should only seek care if they are worsening or if an alarm symptom, such as high fever, bloody or rusty sputum, or shortness of breath, occurs. Careful selection of the words used to describe the infection is also important [144]. One survey showed that patients were less dissatisfied after not receiving antibiotics for a chest cold or ''viral upper respiratory infection'' than they were for acute bronchitis [144].

The use of delayed antibiotic prescription or ''wait-and-see'' prescriptions, which are given to patients with instructions to fill them only if symptoms do not resolve within a specific timeframe, have also been shown to reduce antibiotic use [145, 146]. In a randomised trial comparing either immediate or delayed antibiotic treatment (inviting patients to collect the prescription in the healthcare centre reception after 1 week if required), 55% of the cases in the delayed arm did not pick up their prescriptions [147]. In another trial, which tested the effectiveness of three prescribing strategies and an information leaflet for acute lower respiratory tract infections, LITTLE *et al.* [88] observed that only 20% of patients receiving a delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection actually took them. In a randomised trial of a patient information leaflet in patients with acute bronchitis for whom antibiotics were judged to

be unnecessary by their general practitioner, the leaflet reduced uptake compared to those without any information among patients receiving delayed prescription of antibiotics (49% *versus* 63%; RR 0.76) [145]. However, the actual consumption of antibiotics with the use of the delayed prescription of antibiotics might have been overestimated with the results obtained in randomised clinical trials, since a recent observational study showed a reduction in antibiotic use of 45% in patients with acute cough who undertook the delayed prescription compared to those who were immediately treated [148]. In a Cochrane Review evaluating different outcomes of delayed prescription of antibiotics in respiratory tract infections compared to immediate prescribing or no-antibiotics strategies, delayed antibiotics were not shown to be different to no antibiotics in terms of symptom control, such as fever and cough, and disease complications [149]. In addition, patient satisfaction was slightly reduced in the delayed antibiotic group compared to the immediate antibiotic group and was similar between delayed and no-antibiotic groups. It therefore seems reasonable that in patients with uncomplicated acute bronchitis for whom clinicians feel it is safe not to prescribe antibiotics immediately, no antibiotics with advice to return if symptoms do not resolve is likely to result in the least antibiotic use, while maintaining similar patient satisfaction and clinical outcomes to delayed antibiotics [149].

In a recent editorial, LINDER [150] stated that we should reduce the amount of antibiotics prescribed for patients with acute cough to 10%; however, this seems unrealistic. On average, the effect of these interventions in reducing antibiotic prescription for patients with acute bronchitis is not very large and only with a great deal of effort and multifaceted interventions involving interactive educational materials for physicians, enhancing communication skills and introducing valid point-of-care rapid testing in consultations are we able to reduce the percentage of antibiotics to 20%. In my opinion, there is no doubt that reducing the antibiotic prescribing rate to 20% among patients with acute bronchitis would constitute success.

Statement of Interest

C. Llor has received research grants from the European Commission (Sixth and Seventh Programme Frameworks), Catalan Society of Family Medicine and Instituto de Salud Carlos III (Spanish Ministry of Health).

References

1. Macfarlane J, Holmes W, Gard P, *et al.* Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001; 56: 109–114.
2. Albert RH. Diagnosis and treatment of acute bronchitis. *Am Fam Physician* 2010; 82: 1345–1250.
3. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections – full version. *Clin Microbiol Infect* 2011; 17: Suppl. 6, E1–E59.
4. Ashworth M, Charlton J, Ballard K, *et al.* Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995–2000. *Br J Gen Pract* 2005; 55: 603–608.
5. Worrall G. Acute bronchitis. *Can Fam Physician* 2008; 54: 238–239.
6. Ayres JG. Seasonal pattern of acute bronchitis in general practice in the United Kingdom 1976–83. *Thorax* 1986; 41: 106–110.
7. Chalmers JD, Hill AT. Investigation of "non-responding" presumed lower respiratory tract infection in primary care. *BMJ* 2011; 343: d5840.
8. Oeffinger KC, Snell LM, Foster BM, *et al.* Diagnosis of acute bronchitis in adults: a national survey of family physicians. *J Fam Pract* 1997; 42: 402–409.
9. Kicska G, Zhuang H, Alavi A. Acute bronchitis imaged with F-18 FDG positron emission tomography. *Clin Nucl Med* 2003; 28: 511–512.
10. Williamson HA Jr. Pulmonary function tests in acute bronchitis: evidence for reversible airway obstruction. *J Fam Pract* 1987; 25: 251–256.
11. Thiadens HA, de Bock GH, Dekker FW, *et al.* Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. *BMJ* 1998; 316: 1286–1290.
12. Boivin G, Abed Y, Pelletier G, *et al.* Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. *J Infect Dis* 2002; 186: 1330–1334.
13. Bastien N, Ward D, Van Caeseele P, *et al.* Human metapneumovirus infection in the Canadian population. *J Clin Microbiol* 2003; 41: 4642–4646.

14. Louie JK, Hacker JK, Gonzales R, *et al.* Characterization of viral agents causing acute respiratory infection in a San Francisco University Medical Center Clinic during the influenza season. *Clin Infect Dis* 2005; 41: 822–828.
15. Freymuth F, Vabret A, Gouarin S, *et al.* Épidémiologie et diagnostic des infections à virus respiratoire syncytial de l'adulte. [Epidemiology and diagnosis of respiratory syncytial virus in adults.] *Rev Mal Respir* 2004; 21: 35–42.
16. Gencay M, Roth M, Christ-Crain M, *et al.* Single and multiple viral infections in lower respiratory tract infection. *Respiration* 2010; 80: 560–567.
17. Macfarlane JT, Colville A, Guion A, *et al.* Prospective study of aetiology and outcome of adult lower-respiratory tract infections in the community. *Lancet* 1993; 341: 511–514.
18. Henry D, Ruoff GE, Rhudy J, *et al.* Effectiveness of short-course therapy (5 days) with cefuroxime axetil in treatment of secondary bacterial infections of acute bronchitis. *Antimicrob Agents Chemother* 1995; 39: 2528–2534.
19. Laurenzi GA, Potter RT, Kass EH. Bacteriologic flora of the lower respiratory tract. *N Engl J Med* 1961; 265: 1273–1278.
20. Smith JMB, Lockwood BM. Commensal or pathogen? The growing dilemma facing the general practitioner. *NZ Med J* 1986; 99: 242–243.
21. Boldy DAR, Skidmore SJ, Ayres JG. Acute bronchitis in the community: clinical features, infective factors, changes in pulmonary function and bronchial reactivity to histamine. *Respir Med* 1990; 84: 377–385.
22. Stuart-Harris CH, Andrewes C, Andrews BE, *et al.* A collaborative study of the aetiology of acute respiratory infections in Britain 1961–4. *Br Med J* 1965; 29: 319–326.
23. King DE, Williams WC, Bishop L, *et al.* Effectiveness of erythromycin in the treatment of acute bronchitis. *J Fam Pract* 1996; 42: 601–605.
24. Foy HM. Infections caused by *Mycoplasma pneumoniae* and possible carrier state in different populations of patients. *Clin Infect Dis* 1993; 17: 37–46.
25. Falck G, Heyman L, Gnarpe J, *et al. Chlamydia pneumoniae* (TWAR): a common agent in acute bronchitis. *Scand J Infect Dis* 1994; 26: 179–187.
26. Grayston JT, Aldous MB, Easton A, *et al.* Evidence that *Chlamydia pneumoniae* causes pneumonia and bronchitis. *J Infect Dis* 1993; 168: 1231–1235.
27. Thom DH, Grayston JE, Campbell LA, *et al.* Respiratory infection with *Chlamydia pneumoniae* in middle-aged and older adult outpatients. *Eur J Clin Microbiol Infect Dis* 1994; 13: 785–792.
28. Herwaldt LA. Pertussis in adults: what physicians need to know. *Arch Intern Med* 1991; 151: 1510–1512.
29. Robertson PW, Goldberg H, Jarvie BH, *et al. Bordetella pertussis* infection: a cause of persistent cough in adults. *Med J Aust* 1987; 146: 522–525.
30. Jonsson JS, Sigurdsson JA, Kristinsson KG, *et al.* Acute bronchitis in adults: how close do we come to its aetiology in general practice? *Scand J Prim Health Care* 1997; 15: 156–160.
31. Evans AS, Brobst M. Bronchitis, pneumonitis, and pneumonia in University of Wisconsin students. *N Engl J Med* 1961; 265: 401–409.
32. Mogabgab WJ. *Mycoplasma pneumoniae* and adenovirus respiratory illnesses in military and university personnel. *Am Rev Respir Dis* 1968; 97: 345–358.
33. Wright SW, Edwards KM, Decker MD, *et al.* Pertussis infection in adults with persistent cough. *JAMA* 1995; 273: 1044.
34. Ward JI, Cherry JD, Chang SJ, *et al.* Efficacy of an acellular pertussis vaccine among adolescents and adults. *N Engl J Med* 2005; 353: 1555–1563.
35. Cherry JD. Epidemic pertussis in 2012 – the resurgence of a vaccine-preventable disease. *N Engl J Med* 2012; 367: 785–787.
36. de Greeff SC, de Melker HE, van Gageldonk PG, *et al.* Seroprevalence of pertussis in the Netherlands: evidence for increased circulation of *Bordetella pertussis. PLoS One* 2010; 5: e14183.
37. Kretzschmar M, Teunis PF, Pebody RG. Incidence and reproduction numbers of pertussis: estimates from serological and social contact data in five European countries. *PLoS Med* 2010; 7: e1000291.
38. Rohani P, Drake JM. The decline and resurgence of pertussis in the US. *Epidemics* 2011; 3: 183–188.
39. Vernacchio L, Kelly JP, Kaufman DW, *et al.* Cough and cold medication use by US children, 1999–2006: results from the Slone survey. *Pediatrics* 2008; 122: e323–e329.
40. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 2012; 4: CD001831.
41. Becker LA, Hom J, Villasis-Keever M, *et al.* β_2-agonists for acute bronchitis. *Cochrane Database Syst Rev* 2011; 7: CD001726.
42. Morice A, Abdul-Manap R. Drug treatments for coughs and colds. *Prescriber* 1998; 9: 74–79.
43. Parvez L, Vaidya M, Sakhardande A, *et al.* Evaluation of antitussive agents in man. *Pulm Pharmacol* 1996; 9: 299–308.
44. Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. *Chest* 2001; 120: 1121–1128.
45. Lee PCL, Jawad MSM, Eccles R. Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory infection. *J Pharm Pharmacol* 2000; 52: 1137–1142.
46. Eccles R, Morris S, Jawad M. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. *J Clin Pharmacy Ther* 1992; 17: 175–180.

47. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. *J Pharm Pharmacol* 1997; 49: 1045–1049.
48. Paul IM, Yoder KE, Crowell KR, *et al.* Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004; 114: e85–e90.
49. Use of codeine- and dextromethorphan-containing cough remedies in children. American Academy of Pediatrics. Committee on Drugs. *Pediatrics* 1997; 99: 918–920.
50. Lokker N, Sanders L, Perrin EM, *et al.* Parental misinterpretations of over-the-counter pediatric cough and cold medication labels. *Pediatrics* 2009; 123: 1464–1471.
51. Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129: Suppl., 95S–103S.
52. Kuhn JJ, Hendley JO, Adams KF, *et al.* Antitussive effect of guaifenesin in young adults with natural colds. *Chest* 1982; 82: 713–718.
53. Robinson RE, Cummings WB, Deffenbaugh ER. Effectiveness of guaifenesin as an expectorant: a cooperative double-blind study. *Curr Ther Res* 1977; 22: 284–296.
54. Nespoli L, Monafo V, Bonetti F, *et al.* Valutazione clínica dell'attivita della letosteina nel trattamento della bronchite acuta febbrile in eta pediatrica. Indagine controllata in doppio cieco vs placebo. [Clinical evaluation of letosteine activity in the treatment of acute febrile bronchitis in children. Double-blind controlled study *versus* placebo.] *Minerva Pediatr* 1989; 41: 515–520.
55. Nesswetha W. Kriterien der Arzneimittelpruefung in der werksaerztlichen Praxis, dargestellt am Beispiel eines Hustenloesers. [Criteria of drug testing in industrial practice, demonstrated by a cough remedy.] *Arzneimittelforschung* 1967; 17: 1324–1326.
56. Paul IM, Yoder KE, Crowell KR, *et al.* Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004; 114: E85–E90.
57. Bjórnsdóttir I, Einarson TR, Gudmundsson LS, *et al.* Efficacy of diphenhydramine against cough in humans: a review. *Pharm World Sci* 2007; 29: 577–583.
58. Raherison C, Poirier R, Daurès JP, *et al.* Lower respiratory tract infections in adults: non-antibiotic prescriptions by GPs. *Respir Med* 2003; 97: 995–1000.
59. Girbino G, Oliani C, Lauriello G, *et al.* Un nuovo antiflogistico-analgesico-antipiretico nel trattamento delle affezioni acute delle vie bronchiali. [A new anti-inflammatory-analgesic-antipyretic for the treatment of acute disease of the bronchi.] *Riv Eur Sci Med Farmacol* 1990; 12: 359–366.
60. Ponsioen BP, Hop WC, Vermue NA, *et al.* Efficacy of fluticasone on cough: a randomised controlled trial. *Eur Respir J* 2005; 25: 147–152.
61. Reiner M. Nimesulide and antibiotics in the treatment of acute infections of the respiratory tract. *Curr Med Res Opin* 1983; 8: 487–492.
62. Ellul-Micallef R. Effect of terbutaline sulphate in chronic "allergic" cough. *BMJ* 1983; 287: 940–943.
63. Melbye H, Kongerud J, Vorland L. Reversible airflow limitation in adults with respiratory infection. *Eur Respir J* 1994; 7: 1239–1245.
64. Littenberg B, Wheeler M, Smith DS. A randomized controlled trial of oral albuterol in acute cough. *J Fam Pract* 1996; 42: 49–53.
65. Hueston WJ. A comparison of albuterol and erythromycin for the treatment of acute bronchitis. *J Fam Pract* 1991; 33: 476–480.
66. Hueston WJ. Albuterol delivered by metered-dose inhaler to treat acute bronchitis. *J Fam Pract* 1994; 39: 437–440.
67. Tukianen H, Karttunen P, Silvasti M, *et al.* The treatment of acute transient cough: a placebo-controlled comparison of dextromethorphan and dextromethorphan-beta2-sympathomimetic combination. *Eur J Respir Dis* 1986; 69: 95–99.
68. Melbye H, Aasebo U, Straume B. Symptomatic effect of inhaled fenoterol in acute bronchitis: a placebo-controlled double-blind study. *Fam Pract* 1991; 8: 216–222.
69. Bernard DW, Goepp JG, Duggan AK, *et al.* Is oral albuterol effective for acute cough in nonasthmatic children? *Acta Pediatr* 1999; 88: 465–467.
70. Korppi M, Pietikainen M, Laurikainen K, *et al.* Antitussives in the treatment of acute transient cough in children. *Acta Pediatr Scand* 1991; 80: 969–971.
71. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000; 2: CD001107.
72. Yale SH, Liu K. *Echinacea purpurea* therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* 2004; 164: 1237–1241.
73. Timmer A, Günther J, Rücker G, *et al. Pelargonium sidoides* extract for acute respiratory tract infections. *Cochrane Database Syst Rev* 2008; 3: CD006323.
74. Chuchalin AG, Berman B, Lehmacher W. Treatment of acute bronchitis in adults with a pelargonium sidoides preparation (EPs 7630): a randomized, double-blind, placebo-controlled trial. *Explore (NY)* 2005; 1: 437–445.
75. Matthys H, Eisebitt R, Seith B, *et al.* Efficacy and safety of an extract of Pelargonium sidoides (EPs 7630) in adults with acute bronchitis. A randomised, double-blind, placebo-controlled trial. *Phytomedicine* 2003; 10: 7–17.
76. Teschke R, Frenzel C, Wolff A, *et al.* Initially purported hepatotoxicity by Pelargonium sidoides: the dilemma of pharmacovigilance and proposals for improvement. *Ann Hepatol* 2012; 11: 500–512.

77. Jiang L, Li K, Wu T. Chinese medicinal herbs for acute bronchitis. *Cochrane Database Syst Rev* 2012; 2: CD004560.
78. Oduwole O, Meremikwu MM, Oyo-Ita A, *et al.* Honey for acute cough in children. *Cochrane Database Syst Rev* 2012; 3: CD007094.
79. Paul IM, Beiler J, McMonagle A, *et al.* Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. *Arch Pediatr Adolesc Med* 2007; 161: 1140–1146.
80. Shadram MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents. *J Altern Compliment Med* 2010; 16: 787–793.
81. Wenzel RP, Fowler AA. Clinical practice. Acute bronchitis. *N Engl J Med* 2006; 355: 2125–2130.
82. Smith SM, Fahey T, Smucny J, *et al.* Antibiotics for acute bronchitis. *Cochrane Database Syst Rev* 2012; 4: CD000245.
83. Brickfield FX, Carter WH, Johnson RE. Erythromycin in the treatment of acute bronchitis in a community practice. *J Fam Pract* 1986; 23: 119–122.
84. Dunlay J, Reinhardt R, Roi LD. A placebo-controlled, double-blind trial of erythromycin in adults with acute bronchitis. *J Fam Pract* 1987; 25: 137–141.
85. Franks P, Gleiner JA. The treatment of acute bronchitis with trimethoprim and sulfamethoxazole. *J Fam Pract* 1984; 19: 185–190.
86. Howie JGR, Clark GA. Double-blind trial of early demethychlortetracycline in minor respiratory illness in general practice. *Lancet* 1970; 28: 1099–1102.
87. Kaiser L, Lew D, Hirschel B, *et al.* Effects of antibiotic treatment in the subset of common-cold patients who have bacteria in nasopharyngeal secretions. *Lancet* 1996; 347: 1507–1510.
88. Little P, Rumsby K, Kelly J, *et al.* Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection. *JAMA* 2005; 293: 3029–3035.
89. Matthys H, de Mey C, Carls C, *et al.* Efficacy and tolerability of myrtol standardised in acute bronchitis. *Arzmeimittelforschung* 2000; 50: 700–711.
90. Nduba VN, Mwachari CW, Magaret AS, *et al.* Placebo found equivalent to amoxicillin for treatment of acute bronchitis in Nairobi, Kenya: a triple blind, randomised equivalence study. *Thorax* 2008; 63: 999–1005.
91. Scherl ER, Riegler SL, Cooper JK. Doxycycline in acute bronchitis: a randomized double-blind trial. *J Ky Med Assoc* 1987; 85: 539–541.
92. Verheij TJM, Hermans J, Mulder JD. Effects of doxycycline in patients with acute cough and purulent sputum: a double blind placebo controlled trial. *Br J Gen Pract* 1994; 44: 400–404.
93. Williamson HA. A randomized controlled trial of doxycycline in the treatment of acute bronchitis. *J Fam Pract* 1984; 19: 481–486.
94. Stott NC, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. *Br Med J* 1976; 2: 556–559.
95. Evans AT, Husain S, Durairaj L, *et al.* Azithromycin for acute bronchitis: a randomised double-blind, controlled trial. *Lancet* 2002; 359: 1648–1654.
96. van Vogt S, Brockhuizen L, Zuithoff N, *et al.* Incidental chest radiographs findings in adult patients with acute cough. *Ann Fam Med* 2012; 10: 510–515.
97. Little P, Stuart B, Moore M, *et al.* Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013; 13: 123–129.
98. Smucny JJ, Becker LA, Glazier RH, *et al.* Are antibiotics effective treatment for acute bronchitis? A meta-analysis. *J Fam Pract* 1998; 47: 453–460.
99. Centre for Clinical Practice at NICE. Respiratory Tract Infections – Antibiotic Prescribing: Prescribing of Antibiotics for Self-Limiting Respiratory Tract Infections in Adults and Children in Primary Care. London, National Institute for Health and Clinical Excellence, 2008.
100. Snow V, Mottur-Pilson C, Gonzales R. Principles of appropriate antibiotic use for treatment of acute bronchitis in adults. *Ann Intern Med* 2001; 134: 518–520.
101. Butler CC, Dunstan F, Heginbothom M, *et al.* Containing antibiotic resistance: decreased antibiotic-resistant coliform urinary tract infections with reduction in antibiotic prescribing by general practices. *Br J Gen Pract* 2007; 57: 785–792.
102. Cosby JL, Francis N, Butler CC. The role of evidence in the decline of antibiotic use for common respiratory infections in primary care. *Lancet Infect Dis* 2007; 7: 749–756.
103. Coco A, Mainous AG. Relation of time spent in an encounter with the use of antibiotics in pediatric office visits for viral respiratory infections. *Arch Pediatr Adolesc Med* 2005; 159: 1145–1149.
104. Linder JA, Singer DE, Stafford RS. Association between antibiotic prescribing and visit duration in adults with upper respiratory tract infections. *Clin Ther* 2003; 25: 2419–2430.
105. Mainous AG 3rd, Zoorob RH, Hueston WJ. Current management of acute bronchitis in ambulatory care: the use of antibiotics and bronchodilators. *Arch Fam Med* 1996; 5: 79–83.
106. Macfarlane JT, Worboys M. The changing management of acute bronchitis in Britain, 1940–1970: the impact of antibiotics. *Med Hist* 2008; 52: 47–72.

107. Linder JA. Editorial commentary: antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. *Clin Infect Dis* 2008; 47: 744–746.
108. Gonzales R, Malone DC, Maselli JH, *et al.* Excessive antibiotic use for acute respiratory infections in the United States. *Clin Infect Dis* 2001; 33: 757–762.
109. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 1997; 278: 901–904.
110. Meza RA, Bridges-Webb C, Sayer GP, *et al.* The management of acute bronchitis in general practice: results from the Australian morbidity and treatment survey, 1990–1991. *Austr Fam Physician* 1994; 23: 1550–1553.
111. Straand J, Skinio Rokstad K, Sandvik H. Prescribing systemic antibiotics in general practice: a report from the Møre and Romsdal Prescription Study. *Scand J Prim Health Care* 1998; 16: 121–127.
112. Petersen I, Johnson AM, Islam A, *et al.* Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007; 335: 982.
113. Grover ML, Mookadam M, Rutkowski RH, *et al.* Acute respiratory tract infection: a practice examines its antibiotic prescribing habits. *J Fam Pract* 2012; 61: 330–335.
114. Butler CC, Kelly MJ, Hood K, *et al.* Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection. *Eur Respir J* 2011; 38: 119–125.
115. Coenen S, Michiels B, Renard D, *et al.* Antibiotic prescribing for acute cough: the effect of perceived patient demand. *Br J Gen Pract* 2006; 56: 183–190.
116. Fischer T, Fischer S, Kochen MM, *et al.* Influence of patient symptoms and physical findings on general practitioners' treatment of respiratory tract infections: a direct observation study. *BMC Fam Pract* 2005; 6: 6.
117. Hummers-Pradier E, Pelz J, Himmel W, *et al.* Treatment of respiratory tract infections: a study in 18 general practices in Germany. *Eur J Gen Pract* 1999; 5: 15–20.
118. Akkerman AE, Kuyvenhoven MM, van der Wouden JC, *et al.* Determinants of antibiotic overprescribing in respiratory tract infections in general practice. *J Antimicrob Chemother* 2005; 56: 930–936.
119. Gonzales R, Barrett PH, Steiner JF. The relation between purulent manifestations and antibiotic treatment of upper respiratory tract infections. *J Gen Intern Med* 1999; 14: 151–156.
120. Dosh SA, Hickner JM, Mainous AG, *et al.* Predictors of antibiotic prescribing for nonspecific upper respiratory infections, acute bronchitis, and acute sinusitis – an UPRNet study. *J Fam Pract* 2000; 49: 407–414.
121. Dunlay J, Reinhardt R. Clinical features and treatment of acute bronchitis. *J Fam Pract* 1984; 18: 719–722.
122. Miravitlles M, Kruesmann F, Haverstock D, *et al.* Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012; 39: 1354–1360.
123. Altiner A, Wilm S, Daubener W, *et al.* Sputum colour for diagnosis of a bacterial infection in patients with acute cough. *Scand J Prim Health* 2009; 27: 70–73.
124. Stanton N, Hood K, Kelly MJ, *et al.* Are smokers with acute cough in primary care prescribed antibiotics more often, and to what benefit? An observational study in 13 European countries. *Eur Respir J* 2010; 35: 761–767.
125. Altunaiji SM, Kukuruzovic RH, Curtis NC, *et al.* Antibiotics for whooping cough. *Cochrane Database Syst Rev* 2011; 7: CD004404.
126. Coenen S, Goossens H. Antibiotics for respiratory tract infections in primary care. *BMJ* 2007; 335: 946–947.
127. Anthonisen NR, Manfreda J, Warren CPW, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
128. Llor C, Moragas A, Hernández S, *et al.* Efficacy of antibiotic therapy for acute exacerbations of mild to moderate COPD. *Am J Respir Crit Care Med* 2012; 186: 716–723.
129. Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of published and unpublished clinical trials. *Fam Pract* 2013; 30: 125–133.
130. Jefferson T, Jones MA, Doshi P, *et al.* Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012; 1: CD008965.
131. Godlee F. Open letter to Roche about oseltamivir trial data. *BMJ* 2012; 345: e7305.
132. Linder JA, Nieva HR, Blumentals WA. Antiviral and antibiotic prescribing for influenza in primary care. *J Gen Intern Med* 2009; 24: 504–510.
133. Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005; 4: CD003539.
134. van der Velden AW, Pijpers EJ, Kuyvenhoven MM, *et al.* Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. *Br J Gen Pract* 2012; 62: 801–807.
135. Cals JW, Butler CC, Hopstaken RM, *et al.* Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ* 2009; 338: b1374.
136. Cals JW, Schot MJ, de Jong SA, *et al.* Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Ann Fam Med* 2010; 8: 124–133.
137. Hopstaken RM, Muris JW, Knottnerus JA, *et al.* Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *Br J Gen Pract* 2003; 53: 358–364.

138. Flanders SA, Stein J, Shochat G, *et al.* Performance of a bedside C-reactive protein test in the diagnosis of community-acquired pneumonia in adults with acute cough. *Am J Med* 2004; 116: 529–535.
139. Butler CC, Simpson SA, Dunstan F, *et al.* Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012; 344: d8173.
140. Francis NA, Butler CC, Hood K, *et al.* Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. *BMJ* 2009; 339: b2885.
141. Gonzales R, Anderer T, McCulloch CE, *et al.* A cluster randomized trial of decision support strategies for reducing antibiotic use in acute bronchitis. *JAMA Intern Med* 2013; 173: 267–273.
142. Ebell MH, Lundgren J, Youngpairoj S. How long does a cough last? Comparing patients' expectations with data from a systematic review of the literature. *Ann Fam Med* 2013; 11: 5–13.
143. Cals JW, Scheppers NA, Hosptaken RM, *et al.* Evidence based management of acute bronchitis; sustained competence of enhanced communication skills acquisition in general practice. *Patient Educ Couns* 2007; 68: 270–278.
144. Phillips TG, Hickner J. Calling acute bronchitis a chest cold may improve patient satisfaction with appropriate antibiotic use. *J Am Board Fam Pract* 2005; 18: 459–463.
145. Macfarlane J, Holmes W, Gard P, *et al.* Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. *BMJ* 2002; 324: 91–94.
146. Couchman GR, Rascoe TG, Forjuoh SN. Back-up antibiotic prescriptions for common respiratory symptoms. Patient satisfaction and fill rates. *J Fam Pract* 2000; 49: 907–913.
147. Dowell J, Pitkethly M, Bain J, *et al.* A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. *Br J Gen Pract* 2001; 51: 200–205.
148. Francis NA, Gillespie D, Nuttall J, *et al.* Delayed antibiotic prescribing and associated antibiotic consumption in adults with acute cough. *Br J Gen Pract* 2012; 62: e639–e646.
149. Spurling GKP, Del Mar CB, Dooley L, *et al.* Delayed antibiotics for respiratory infections. *Cochrane Database Syst Rev* 2011; 1: CD004417.
150. Linder JA. Antibiotic prescribing for acute respiratory infections – success that's way off the mark. *JAMA Intern Med* 2013; 173: 273–275.

Chapter 2

Chronic bronchitis: a risk factor for bronchial infection

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SUMMARY: Chronic bronchitis is a clinical entity characterised by chronic bronchial mucus hypersecretion. It is frequently associated with chronic obstructive pulmonary disease (COPD) and it is related to worse outcomes. COPD patients with chronic bronchitis experienced accelerated lung function decline and an increased risk of exacerbations. Chronic mucus hypersecretion is also associated with acute or chronic bacterial bronchial infection, and increased airway and systemic inflammation. In addition, different antibiotic and anti-inflammatory treatments have been tested in these patients, with conflicting results. Mechanisms to explain the relationship between chronic bronchitis and infection are not well established, although host factors have been identified as key factors in the pathogenesis of bronchial infection. This chapter discusses the association of chronic bronchitis and the risk of bronchial infection, and the infection mechanisms that are responsible for this association, potential antibiotic and anti-inflammatory treatment.

KEYWORDS: Acute exacerbation, airway inflammation, bronchial infection, chronic bronchitis, chronic obstructive pulmonary disease, host factors

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Eur Respir Monogr 2013; 60: 18–26.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017012
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Chronic bronchitis is a clinical entity characterised by cough and mucus hypersecretion. It is very common in patients affected by chronic obstructive pulmonary disease (COPD), especially in those with frequent exacerbations [1, 2]. COPD is one of the leading causes of morbidity and mortality worldwide [3]. It is projected that COPD will become the third leading cause of death worldwide in 2020 [4].

Mucus hypersecretion is a result of goblet cell hyperplasia and submucosal gland hypertrophy in large and small airways, and worsens airflow obstruction. Chronic mucus hypersecretion has been shown in some large epidemiological studies to be associated with an accelerated lung function decline and an increased risk of COPD exacerbation [5, 6]. Bronchial hypersecretion has also been related to increased airway inflammation and increased risk of bacterial infection [7, 8]. In addition, different studies have postulated an association of excess mucus secretion with an

elevated risk of bronchial colonisation and bacterial infections [5, 9]. The most recent and relevant data regarding chronic bronchitis and its relationship with bronchial infection are reviewed in this chapter.

Chronic bronchitis

Chronic bronchitis is defined as ''chronic or recurrent excessive mucous secretion in the bronchial tree'' and is diagnosed clinically by the presence of cough and/or chronic expectoration for more than 3 months during at least two consecutive years [10].

The most important aetiological factor is tobacco smoke. Other aetiological factors related to chronic bronchitis are other inflammatory airway diseases, such as bronchiectasis or cystic fibrosis and viral infections [11], or inflammatory cell activation of mucin gene transcription [12]. Chronic bronchitis is compounded by difficulty in clearing secretions because of poor ciliary function, distal airway occlusion and ineffective cough [7, 12, 13]. In smokers, if chronic bronchitis is associated with irreversible airflow obstruction, it is considered a major manifestation of COPD [10, 14]. There is limited information about the prevalence of chronic bronchtis in COPD patients. Recent studies have demonstrated that chronic bronchitis is present in 14–27% of COPD patients [1, 2]. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study, AGUSTI *et al.* [15] showed that 35% of patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II–IV COPD had chronic bronchitis symptoms.

Pathological changes in the respiratory tract of chronic bronchitis patients are shown in table 1 [16–18]. Studies have demonstrated the presence of airway epithelial cells hyperplasia, mucous cell hyperplasia, airway submucosal gland hypertrophy, and mucosal and parenchymal inflammation [19]. In addition, recent studies have shown an increase in mucous cell numbers *via* proliferation and enhanced mucus synthesis and secretion, both in large and small airways [1, 20]. However, the relationship between histopathological changes and mucus hypersecretion is not well established [16, 21].

Chronic bronchitis has been associated with worse outcomes in COPD patients. Studies have demonstrated an increased risk of COPD exacerbation in patients with chronic bronchitis [6, 22–24]. The COPDGene study showed that chronic bronchitis in patients with COPD was associated with worse respiratory symptoms and a higher risk of exacerbations [1]. The authors demonstrated that among patients with COPD and similar lung function, those with chronic bronchitis were younger, had a greater smoking history and had a greater likelihood of current smoking history than COPD subjects without chronic bronchitis. Moreover, those with chronic bronchitis had higher St George's Respiratory Questionnaire (SGRQ) scores, a greater degree of breathlessness and more upper airway symptoms. Finally, there was a worse history of exacerbation in the chronic bronchitis group, and more subjects reported severe exacerbations that required hospitalisation or an urgent care visit [1]. The PLATINO (Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar) study has recently showed that chronic bronchitis in COPD patients, defined as the presence of phlegm on most days at least 3 months per year for two or more years, is also associated with worse outcomes [2]. In this study, patients with COPD and chronic bronchitis had more severe disease (worse lung function, more respiratory symptoms and more exacerbations). They also had worse general health status and more physical activity limitation. After adjusting for several potential confounders, the authors concluded that chronic bronchitis in COPD

Table 1. Histopathological changes associated with chronic bronchitis

Enlargement of bronchial mucous glands
Airway epithelial hyperplasia
Airway mucous cell hyperplasia
Airway submucosal gland hypertrophy
Intraluminal inflammation
Mucosal inflammation
Parenchymal inflammation
Increased mucous cells

was associated with wheezing, dyspnoea, higher smoking exposure, worse general health status, lower age and higher use of any respiratory medication.

In addition, international guidelines for the management and treatment of COPD have recently described the importance of establishing different groups of COPD patients (COPD phenotypes) depending on symptoms. Identifying those COPD patients with chronic bronchitis may be crucial to determining specific treatments, including antibiotics or anti-inflammatory agents [25].

Airway and systemic inflammation

COPD is an inflammatory disease characterised by chronic local (airway) and systemic (serum) inflammation [26]. Several studies have demonstrated increased levels of different inflammatory biomarkers, such as white blood cells, C-reactive protein, reactive oxygen metabolites, tumour necrosis factor-α, and interleukin (IL)-6 and IL-4 in the airways of COPD patients [27–30]. In addition, elevated circulating levels of these inflammatory markers have been reported in COPD patients [30–32]. These findings suggest that persistent inflammation (both local and systemic) may play a significant pathogenic role in COPD [33, 34].

Limited data are available regarding the impact of chronic bronchitis in airway and systemic inflammation. MULLEN *et al.* [35] studied surgically resected specimens of patients with chronic bronchitis and compared them with controls without chronic bronchitis. The authors demonstrated that patients with chronic bronchitis had greater inflammation on the mucosal surfaces of all bronchi larger than 2 mm luminal diameter and on gland ducts in bronchi larger than 4 mm diameter. In addition, MULLEN *et al.* [35] found that inflammation of cartilaginous airways best separated those patients with chronic bronchitis from controls, while differences in inflammation were directly related to the diameter of airways and were more pronounced in larger airways. In 1995, RIISE *et al.* [27] showed that COPD patients had higher levels of myeloperoxidase (MPO), IL-8, hyaluronan and eosinophil cationic protein (ECP) in bronchial lavage fluid when compared with patients without COPD. In this study, the authors also observed a tendency towards higher levels of these inflammatory markers in patients with chronic bronchitis and COPD compared with nonobstructive chronic bronchitis [27].

Other studies evaluated the presence of potentially pathogenic microorganisms (PPMs) with increased levels of inflammatory markers in patients with clinically stable COPD with chronic bronchitis. MONSÓ *et al.* [36] and ZALACAIN *et al.* [37] demonstrated that 20–40% of the patients with chronic bronchitis had lower airway bacterial colonisation by PPMs. Subsequent studies have related the presence of PPMs with a greater bronchial inflammation in chronic bronchitis and COPD patients. HILL *et al.* [38] demonstrated that bacterial load contributes to airway inflammation in patients with stable chronic bronchitis (most of them with COPD and bronchiectasis). The authors demonstrated that airway bacterial load correlated with different sputum inflammatory markers such as MPO, IL-8, leukotriene B_4 and leukocyte elastase activity. Furthermore, markers of inflammation increased progressively with increasing bacterial load [38]. In severe COPD patients, another study showed that the presence of PPMs was associated with a higher IL-8 levels in sputum [39]. The presence of lower bacterial colonisation in the stable state was related to higher exacerbation frequency [39]. In another study with COPD stable patients, WILKINSON *et al.* [40] showed that airway bacterial load was associated with higher levels of sputum IL-6 and IL-8. In addition, patients with bacterial colonisation experienced an accelerated impairment in their lung function. In particular, bacterial colonisation and higher sputum IL-8 were associated with a greater decline in forced expiratory volume in 1 s (FEV_1) [38–40]. Finally, MARIN *et al.* [41] studied the variability and effects of bronchial colonisation in patients with moderate COPD, most of them (70%) with chronic bronchitis. Bronchial colonisation was observed in 70% of the follow-up examinations and was related to higher levels of IL-1β and IL-12, and to sputum neutrophilia. The presence of a neutrophilic bronchial inflammatory response was associated with a significant decline in FEV_1 during the follow-up.

Bronchial infection

The role of bacterial infection in the pathogenesis and course of chronic bronchitis and COPD has been a matter of controversy in the scientific literature. The frequency of bacterial isolation from sputum was found to be similar in stable COPD or chronic bronchitis and during exacerbation, and there was insufficient evidence to support a role of bacterial infection in chronic bronchitis [42]. However, new molecular, cellular and immunological techniques used to study host–pathogen interaction have been applied in a re-examination of the role of infection in COPD and chronic bronchitis, and there is considerable new evidence that infection is the predominant cause of exacerbations and is a likely contributor to the pathogenesis of COPD [43].

Different studies with improved design and modern methods have established that approximately 50% of exacerbations are caused by bacterial infection [43]. One study using bronchoscopic techniques revealed that bacteria were present in clinically significant concentrations in the airways of 29% of adults with stable COPD and in 54% of adults with exacerbated COPD [44]. Another study reported the presence of *Haemophilus influenzae* in bronchial mucosal biopsy specimens from 87% of patients who were intubated because of exacerbations, as compared with 33% of patients with stable COPD and 0% of healthy controls [45]. In another bronchoscopic study in COPD patients requiring hospitalisation due to severe exacerbation, SOLER *et al.* [46] reported an incidence of 45% of PPMs as a cause of these severe exacerbations. In addition, purulent sputum during an exacerbation was highly correlated with the presence of bacteria in the lower respiratory tract [46]. Recent studies have shown that acquisition of a new strain of PPMs, such as *H. influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* or *Pseudomonas aeruginosa*, detected using molecular techniques is strongly associated with the occurrence of an exacerbation [47–51]. All these findings suggest that bacterial infection is a dynamic and complex process that plays an important role in the pathogenesis of exacerbations of COPD [43].

Acute exacerbations of COPD (AECOPD), which are usually associated with chronic bronchitis, cause substantial morbidity and mortality, and marked reduction in quality of life [52–55], placing a significant burden on both patients and healthcare systems [56–58]. Current treatment guidelines recommend antibiotic therapy for patients with more severe illness and often use acute symptom changes based on Anthonisen criteria of type I (worsening dyspnoea with increased sputum purulence) or II (change in any two of these symptoms) to define this group [3, 59, 60]. Previous studies demonstrated that resolution of bronchial inflammation following acute exacerbation in chronic bronchitis is related to bacterial eradication [61]. In this study, WHITE *et al.* [61] showed that those patients in whom bacteria continue to be cultured from their sputum after antibiotic treatment have partial resolution of the inflammation, which may reflect continued stimulation by the reduced bacterial load. The MAESTRAL (Moxifloxacin in Acute Exacerbations of Chronic Bronchitis Trial) study [62] confirmed that bacterial eradication at the end of antibiotic therapy was associated with higher clinical cure rates at 8 weeks post-therapy. This study included patients with COPD and chronic bronchitis suffering from an Anthonisen type I exacerbation.

In order to decrease the frequency of exacerbations using antibiotic treatment, the PULSE study evaluated the effect of intermittent pulsed therapy with a respiratory fluoroquinolone (moxifloxacin) in stable patients with COPD and chronic bronchitis with previous acute exacerbations [63]. This study found that preventive antibiotic treatment was effective, especially in those COPD patients with purulent or mucopurulent sputum at baseline. These findings suggest that prevention of acute and chronic infection in COPD would be indicated in patients with chronic bronchitis with mucopurulent sputum production and a history of frequent exacerbations despite proper inhaled bronchodilator treatment. In addition, ALBERT *et al.* [64] performed a randomised clinical trial to determine whether azithromycin decreases the frequency of exacerbations in COPD. This study concluded that among selected patients (with previous exacerbations or who require supplemental oxygen), adding azithromycin to usual treatment decreased the frequency of exacerbations and improved quality of life in COPD. However, other studies have related the use of macrolides to a higher risk of cardiovascular death [65].

Inhaled antibiotics may have a potential role in these patients, although evidence in COPD is still scarce [66]. DAL NEGRO *et al.* [67] studied the effect of inhaled tobramycin in 13 severe COPD patients with multiresistant *P. aeruginosa* colonisation. These authors found a reduction of pro-inflammatory mediator levels (IL-1β, IL-8 and eosinophils) and a decrease in severe exacerbations in patients treated with inhaled tobramycin. In addition, STEINFORT and STEINFORT [68] showed a reduction in FEV1 decline in patients with bronchiectasis or severe COPD with multiresistant Gram-negative bacterial chronic infection who received nebulised colistin. Further studies are needed to establish a routine use of aerosolised antibiotics in COPD patients, particularly in those with chronic bronchitis.

Recent studies have postulated that COPD with chronic bronchitis and frequent exacerbations may also be treated with anti-inflammatory drugs, such as inhaled corticosteroids and/or the phosphodiesterase 4 (PDE4) inhibitor roflumilast. This PDE4 inhibitor has been shown to improve lung function in moderate and severe COPD [25, 69], and to prevent COPD exacerbations in those patients with chronic cough and expectoration [69, 70]. This effect is maintained when roflumilast is added to long-acting bronchodilators and achieves an increase in FEV1 higher than with salmeterol or tiotropium [71, 72].

Infection mechanisms

The reasons why some patients with chronic bronchitis become infected and others do not are not well established. Both pathogenic and host factors determine the outcome of acquisition of a bacterial strain. Not all acquisitions of pathogenic bacteria are followed by exacerbations. FERNAAYS *et al.* [73] showed that different genome contents of nontypeable *H. influenzae* (NTHi) were associated with the ability to cause exacerbations in COPD. In addition, strains of *H. influenzae* that cause exacerbations showed increased adherence to epithelial cells, increased induction of IL-8 and increased neutrophil recruitment, compared with colonising strains [74].

Table 2. Humoral substances produced by airway epithelial cells

Inflammatory mediators
Cytokines
Chemokines
Leukotrienes
Calprotectin
Chemotactic factors
Mucins
Secreted IgA
LL-37/CAP-18
β-defensins
Chemokines
Leukotrienes
Antimicrobial agents
β-defensins
LL-37/CAP-18
Lysozyme
Lactoferrin
SPLI
Elafin
Calprotectin
Phospholipase A_2
SP-A, SP-D
Anionic peptides

LL-37/CAP-18: cationic antimicrobial peptides; SPLI: secretory leukocyte proteinase inhibitor; SP: surfactant protein.

Host factors are key determinants in the pathogenesis of a bronchial infection. A failure of innate immune mechanisms in chronic bronchitis allows bacteria to proliferate and persist in the airways [43]. Recent evidence suggests that innate immunity has a pivotal role in respiratory antimicrobial defences. Airway epithelial cells are an active interface that responds to microbial exposure with the production of a variety of small anionic and cationic antimicrobial peptides and antimicrobial proteins that act as "endogenous antibiotics" to combat the inhaled microorganisms [75]. In addition, airway epithelial cells also release cytokines, chemokines and chemotactic factors that attract cells of specific and nonspecific immunity, triggering local inflammatory reactions (table 2) [76].

Recent studies have demonstrated the alteration of some of these humoral substances produced by airway epithelial cells in patients with COPD and its relationship with chronic inflammation and chronic infection. POLOSUKHIN *et al.* [77] showed that COPD patients with bronchial epithelial remodelling had secretory IgA (SIgA) deficiency, reduced polymeric immunoglobulin receptor expression and increased $CD4^+$ and $CD8^+$ lymphocyte infiltration, as compared with bronchial mucosa from controls. These findings suggest an important role of SIgA deficiency with chronic airway

inflammation and disease progression of COPD. Another study conducted by PARAMESWARAN *et al.* [78] demonstrated that COPD patients colonised by *M. catarrhalis* and *H. influenzae* had lower levels of antimicrobial peptides such as lysozyme, lactoferrin, LL-37 and the secretory leukocyte protease inhibitor (SLPI) when compared with COPD patients without bacteria in their airways. In addition, these values were even lower when COPD patients experienced acute exacerbations [78].

As mucus hyperproduction is a distinguishing feature of chronic bronchitis, studies regarding mucins have become very important in the recent years. Mucins are glycoproteins secreted by airway epithelial cells that compose the major macromolecular constituent of the mucus [79–81]. Importantly, secreted mucins also contribute important antimicrobial and anti-inflammatory properties, and may explain differences in clinical features of chronic bronchitis and COPD patients. KIRHAM *et al.* [82] evaluated the major polymeric mucins in COPD patients, as compared with smokers without airflow obstruction. They found that MUC5AC was the predominant mucin in smokers without airflow obstruction, whereas MUC5B was more abundant in the patients with COPD. Furthermore, there was a shift towards smaller mucins in the COPD group. Although further studies are needed to examine how these mucin airway expression changes may impact disease progression, the role of mucins in the pathogenesis of chronic bronchitis is well accepted.

Conclusions

Chronic bronchitis is a clinical entity defined as chronic or recurrent excessive mucous secretion in the bronchial tree and characterised by chronic mucus hypersecretion, which is frequently associated with COPD. Patients with COPD and chronic bronchitis had worse lung function, more respiratory symptoms and more exacerbations. Several studies associated the presence of chronic bronchitis with airway and systemic inflammation, which is also related to worse clinical outcomes. Bronchial hypersecretion has been associated with an increased risk of bronchial colonisation and respiratory infection, which may explain why patients with chronic bronchitis have more inflammation and an increased frequency of exacerbations. Selected cases of frequent exacerbators with chronic bronchitis may respond to long-term antibiotic treatment to prevent exacerbations. Mechanisms by which some patients have PPMs in their airways are not known. Recent studies identified alterations in innate immunological mechanisms that may explain the relationship between chronic bronchitis, inflammation and infection. Further studies are needed to examine how these changes may impact the pathogenesis and progression of the disease.

Statement of Interest

M.I. Restrepo participated in advisory boards for Theravance, Forest Laboratories, Johnson & Johnson, Trius and Novartis, and acted as a consultant for Theravance, Trius and Pfizer (Wyeth). The author's time is partially protected by award number K23HL096054 from the National Heart, Lung, And Blood Institute. A. Anzueto has participated as a speaker in scientific meetings or courses organised and financed by various pharmaceutical companies including Boehringer Ingelheim, Bayer Heahlthcare, GlaxoSmithKline and Forest Laboratories. The author has been a consultant for AstraZeneca, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Bayer Healthcare, Forest Laboratories, Intermune and Amgen. He has been the principal investigator for research grants and the University of Texas Health Science Center at San Antonio, and was paid for participating in multicentre clinical trials sponsored by GlaxoSmithKline, Bayer-Schering Pharma, Lilly and the National Institutes of Health.

References

1. Kim V, Han MK, Vance GB, *et al.* The chronic bronchitis phenotype of COPD: an analysis of the COPDGene study. *Chest* 2011; 140: 626–633.
2. Montes de Oca M, Halbert RJ, López MV, *et al.* The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study. *Eur Respir J* 2012; 40: 28–36.

3. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. www.goldcopd.org Date last updated: December, 2011. Date last accessed: September, 2012.
4. Agusti A, Sobradillo P, Celli B. Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. *Am J Respir Crit Care Med* 2011; 183: 1129–1137.
5. Vestbo J, Prescott E, Lange P, *et al.* Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. *Am J Respir Crit Care Med* 1996; 153: 1530–1535.
6. Seemungal TA, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
7. Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 2645–2653.
8. Kim V, Kelemen SE, Abuel-Haija M, *et al.* Small airway mucous metaplasIa and inflammation in chronic obstructive pulmonary disease. *COPD* 2008; 5: 329–338.
9. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J* 1995; 8: 1333–1338.
10. Fletcher CM, Pride NB. Definitions on emphysema, chronic bronchitis, asthma, and airflow obstruction: 25 years on from the CIBA symposium. *Thorax* 1984; 39: 81–85.
11. Holtzman MJ, Tyner JW, Kim EY, *et al.* Acute and chronic airway responses to viral infection: implications for asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 132–140.
12. Burgel PR, Nadel JA. Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. *Thorax* 2004; 59: 992–996.
13. Verra F, Escudier E, Lebargy F, *et al.* Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and non-smokers. *Am J Respir Crit Care Med* 1995; 151: 630–634.
14. Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet* 1965; 1: 775–781.
15. Agusti A, Calverley PM, Celli B, *et al.* Characterization of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11: 122.
16. Yoshida T, Tuder RM. Pathobiology of cigarette smoke-induced COPD. *Physiol Rev* 2007; 87: 1047–1082.
17. Wright JL, Lawson LM, Pare PD, *et al.* Morphology of peripheral airways in current smokers and ex-smokers. *Am Rev Respir Dis* 1983; 127: 474–477.
18. Thurlbeck WM. Pathology of chronic airflow obstruction. *Chest* 1990; 97: Suppl., S6–S10.
19. Dye JA, Adler KB. Effects of cigarette smoke on epithelial cells of the respiratory tract. *Thorax* 1994; 49: 825–834.
20. Papadaki HA, Velegraki M. The immunology of the respiratory system. *Pneumon* 2007; 20: 384–394.
21. Reid LM. Pathology of chronic bronchitis. *Lancet* 1954; 266: 274–278.
22. Burgel PR, Nesme-Meyer P, Chanez P, *et al.* Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. *Chest* 2009; 135: 975–982.
23. Kim V, Garfield JL, Grabianowski CL, *et al.* Chronic bronchitis symptoms in severe COPD are associated with increased exacerbation frequency and less emphysema. *Am J Respir Crit Care Med* 2009; 179: A1521.
24. Peto R, Speizer FE, Cochrane AL, *et al.* The relevance in adults of air-flow obstruction, but not of mucus hypersecretion, to mortality from chronic lung disease. Results from 20 years of prospective observation. *Am Rev Respir Dis* 1983; 128: 491–500.
25. Miravitlles M, Soler-Cataluña JJ, Calle M, *et al.* Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur Respir J* 2013; 41: 1252–1256.
26. Agusti AG. Systemic effects of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005; 2: 367–370.
27. Riise GC, Ahlstedt S, Larsson S, *et al.* Bronchial inflamation in chronic bronchitis assessed by measurement of cell products in bronchial lavage fluid. *Thorax* 1995; 50: 360–365.
28. Foschino Barbaro MP, Carpagnano GE, Spanevello A, *et al.* Inflammation, oxidative stress and systemic effects in mild chronic obstructive pulmonary disease. *Int J Immunopathol Pharmacol* 2007; 20: 753–763.
29. Comer DM, Kidney JC, Ennis M, *et al.* Airway epithelial cell apoptosis and inflammation in COPD, smokers and nonsmokers. *Eur Respir J* 2013; 41: 1058–1067.
30. Pelegrino NR, Tanni SE, Amaral RA, *et al.* Effects of active smoking on airway and systemic inflammation profiles in patients with chronic obstructive pulmonary disease. *Am J Med Sci* 2012 [In press DOI: 10.1097/MAJ.0b013e31825f32a7].
31. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; 370: 797–799.
32. Gan WQ, Man SF, Senthilselvan A, *et al.* Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; 59: 574–580.
33. Agusti A. Systemic effects of chronic obstructive pulmonary disease: what we know and what we don't know (but should). *Proc Am Thorac Soc* 2007; 4: 522–525.
34. Agusti A, Edwards LD, Rennard SI, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in COPD: A novel phenotype. *PLoS One* 2012; 7: e37483.
35. Mullen JB, Wright JL, Wiggs BR, *et al.* Reassessment of inflammation of airways in chronic bronchitis. *Br Med J* 1985; 291: 1235–1239.

36. Monsó E, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit care Med* 1995; 152: 1316–1320.
37. Zalacain R, Sobradillo V, Amilibia J, *et al.* Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999; 13: 343–348.
38. Hill AT, Campbell EJ, Hill SL, *et al.* Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; 109: 288–295.
39. Patel IS, Seemungal TAR, Wilks M, *et al.* Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax* 2002; 57: 759–764.
40. Wilkinson TMA, Patel IS, Wilks M, *et al.* Airway bacterial load and FEV1 decline in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 167: 1090–1095.
41. Marin A, Monsó E, Garcia-Nuñez M, *et al.* Variability and effects of bronchial colonisation in patients with moderate COPD. *Eur Respir J* 2010; 35: 295–302.
42. Tager I, Speizer PE. Role of infection in chronic bronchitis. *N Engl J Med* 1975; 292: 563–571.
43. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355–2365.
44. Rosell A, Monso E, Soler N, *et al.* Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med* 2005; 165: 891–897.
45. Bandi V, Apicella MA, Mason E, *et al.* Nontypeable *Haemophilus influenzae* in the lower respiratory tract of patients with chronic bronchitis. *Am J Respir Crit Care Med* 2001; 164: 2114–2119.
46. Soler N, Agusti C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 2007; 62: 29–35.
47. Sethi S, Sethi R, Eschberger K, *et al.* Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 356–361.
48. Sethi S, Evans M, Grant BJB, *et al.* New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347: 465–471.
49. Murphy TF, Brauer AL, Sethi S. *Haemophilus haemolyticus*: a human respiratory tract commensal to be distinguished from *Haemophilus influenzae*. *J Infect Dis* 2007; 195: 81–89.
50. Murphy TF, Brauer AL, Grant BJ, *et al. Moraxella catarrhalis* in chronic obstructive pulmonary disease: burden of disease and immune response. *Am J Respir Crit Care Med* 2005; 172: 195–199.
51. Murphy TF, Brauer AL, Eschberger K, *et al. Pseudomonas aeruginosa* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 853–860.
52. Miravitlles M, Ferrer M, Pont A, *et al.* Exacerbations impair quality of life in patients with chronic obstructive pulmonary disease. A 2 year follow-up study. *Thorax* 2004; 59: 387–395.
53. Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax* 2006; 61: 250–258.
54. Wedzicha JA, Donaldson GC. Exacerbations of chronic obstructive pulmonary disease. *Respir Care* 2003; 48: 1204–1213.
55. Wilkinson T, Wedzicha JA. Strategies for improving outcomes of COPD exacerbations. *Int J Chron Obstruct Pulmon Dis* 2006; 1: 335–342.
56. Blanchard AR. Treatment of acute exacerbations of COPD. *Clin Cornerstone* 2003; 5: 28–36.
57. Niewoehner DE. The impact of severe exacerbations on quality of life and the clinical course of chronic obstructive pulmonary disease. *Am J Med* 2006; 119: Suppl. 1, S38–S45.
58. Sethi S. Antibiotics in acute exacerbations of chronic bronchitis. *Expert Rev Anti Infect Ther* 2010; 8: 405–417.
59. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J* 2005; 26: 1138–1180.
60. O'Donnell DE, Hernandez P, Kaplan A, *et al.* Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update – highlights for primary care. *Can Respir J* 2008; 15: Suppl. A, 1A–8A.
61. White AJ, Gompertz S, Bayley DL, *et al.* Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58: 680–685.
62. Wilson R, Anzueto A, Miravitlles M, *et al.* Moxifloxacin *versus* amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. *Eur Respir J* 2012; 40: 17–27.
63. Sethi S, Paul WJ, Theron MS, *et al.* Pulsed moxifloxacin for the proevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010; 11: 10.
64. Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–698.
65. Ray WA, Murray KT, Hall K, *et al.* Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012; 366: 1881–1890.
66. Baranda F, Gómez A, Gómez B. Inhaled antibiotic therapy in other respiratory diseases. *Arch Bronconeumol* 2011; 47: 24–29.
67. Dal Negro R, Micheletto C, Tognella S, *et al.* Tobramycin nebulizer solution in severe COPD patients colonized with *Pseudomonas aeruginosa*: effects on bronchial inflammation. *Adv Ther* 2008; 25: 1019–1030.
68. Steinfort DP, Steinfort C. Effect of long-term nebulized colistin on lung function and quality of life in patients with chronic bronchial sepsis. *Intern Med J* 2007; 37: 495–498.

69. Rennard SI, Calverley PMA, Goehring UM, *et al.* Reduction of exacerbations by the PDE4 inhibitor roflumilast: the importance of defining different subsets of patients with COPD. *Respir Res* 2011; 12: 18.
70. Calverley PMA, Sanchez-Toril F, McIvor A, *et al.* Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 154–161.
71. Fabbri LM, Calverley PMA, Izquierdo-Alonso JL, *et al.* Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with long acting bronchodilators: two randomised clinical trials. *Lancet* 2009; 374: 695–703.
72. Bateman ED, Rabe KF, Calverley PM, *et al.* Roflumilast with long-acting β_2-agonists for COPD: influence of exacerbation history. *Eur Respir J* 2011; 38: 553–560.
73. Fernaays MM, Leese AJ, Sethi S, *et al.* Differential genome contents of nontypeable *Haemophilus influenzae* strains from adults with chronic obstructive pulmonary disease. *Infect Immun* 2006; 74: 3366–3374.
74. Chin CL, Manzel LJ, Lehman EE, *et al. Haemophilus influenzae* from patients with chronic obstructive pulmonary disease exacerbation induce more inflammation than colonizers. *Am J Respir Crit Care Med* 2005; 172: 85–91.
75. Papadaki HA, Velegraki M. The immunology of the respiratory system. *Pneumon* 2007; 20: 384–394.
76. Bals R, Hiemstra PS. Innate immunity in the lung: how epithelial cells fight against respiratory pathogens. *Eur Respir J* 2004; 23: 327–333.
77. Polosukhin VV, Cates JM, Lawson WE, *et al.* Bronchial secretory immunoglobulin A deficiency correlates with airway inflammation and progression of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 184: 317–327.
78. Parameswaran GI, Sethi S, Murphy TF. Effects of bacterial infection on airway antimicrobal peptides and proteins in COPD. *Chest* 2011; 140: 611–617.
79. Thornton DJ, Rousseau K, McGuckin MA. Structure and function of the polymeric mucins in airways mucus. *Annu Rev Physiol* 2008; 70: 459–486.
80. Rose MC, Voynow JA. Respiratory tract mucin genes and mucin glycoproteins in health and disease. *Physiol Rev* 2006; 86: 245–278.
81. Voynow JA, Rubin BK. Mucins, mucus and sputum. *Chest* 2009; 135: 505–512.
82. Kirham S, Kolsum U, Rousseau K, *et al.* MUC5B is the major mucin in gel phase of sputum in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 178: 1033–1039.

Chapter 3

Sputum colour: a marker of bacterial infection

Robert A. Stockley

SUMMARY: With the advent of increasing technology, reliance on simple clinical observation has become generally downgraded. However, direct observation and monitoring of sputum colour in patients with and without chronic bronchitis in the stable state and changes during exacerbations provides useful insights into the underlying pathology, nature of any acute exacerbation and the need for antibiotic therapy. Although subjective descriptions can generally be used to withhold antibiotic therapy for acute exacerbations, direct observation and objective grading is more reliable and helps in the delivery of patient directed self-management.

KEYWORDS: Bacteria, chronic obstructive pulmonary disease, neutrophils, sputum

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Eur Respir Monogr 2013; 60: 27–33.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017112
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The confirmation of and changes in bacterial colonisation of the upper bronchial tree pose major logistical questions in the management of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and in identifying the need for antibiotics especially, in bronchiectasis, the absence and presence of cystic fibrosis (CF). Under the heading of sputum assessment, most major textbooks cover the role of routine microbiology and the rapidly evolving field of molecular identification, reflecting the current trends in medicine in general and the reduced reliance on clinical skills.

Sputum is a mixture of expectorated airway secretions variability contaminated with oropharyngeal secretions, but the characteristics of mucus viscosity, mucus plugs, bronchial casts, Curschmann's spirals and broncholiths have all been recognised as markers of specific processes taking place in the airways. The colour and nature of sputum have long been recognised as features that also represent distinct pathophysiological processes, some of which remain well recognised and others that seemed to have slipped from clinical acumen.

The pink frothy sputum of acute left ventricular failure and the presence of streaky or frank haemoptysis provide clear guidance to the underlying processes. Less well recognised colours are the black (although logical) nature of coal dust and pneumoconiosis and the redcurrant jelly of *Klebsiella pneumoniae*, although the rusty coloured sputum of pneumoccocal pneumonia remains well recognised probably because of its prevalence. The ''anchovy sauce'' nature of sputum from patients with hepatobronchial fistulae due to *Entamoeba histolytica* is probably remembered but rarely seen in Northern European countries. However, the same description of ''dirty salmon-pink anchovy sauce'' coloured sputum was noted during World War I in healthy military personnel who had post-influenza staphylococcal pneumonia leading to rapid progression and death [1].

The exacerbation revolution

The increasing prevalence of COPD and the danger of acute exacerbations, especially when associated with acute hospital admissions, places not just a financial burden on healthcare services but also one on decision making in the management of the episodes. The tendency has been to treat these episodes with nebulised bronchodilator combinations, oral corticosteroids and antibiotics to cover any bacterial ''infective'' component whilst awaiting the perceived support of routine microbiology. However, in view of continuing development of antibiotic-resistant strains, there is increasing activity to develop more rapid tests to identify bacterial strains contributing to the acute episodes through molecular technology and blood biomarkers such as pro-calcitonin in an attempt to limit antibiotic prescribing. However, both approaches have their drawbacks.

Molecular technology is a powerful tool to detect low numbers of both viable and non-viable bacteria. Thus, although quantitative methodology can be applied, the results need careful validation against clinical presentation and treatment responses. However, results can be obtained rapidly and potentially also provide information on resistant genes that will facilitate antibiotic choice. Pro-calcitonin is a recognised calcitonin precursor produced by neuro-endocrine cells of the thyroid. However, bacterial products and pro-inflammatory cytokines can stimulate its production systemically [2]. For these reasons, it has been utilised to guide antibiotic therapy in patients with AECOPD. Unfortunately, few studies have compared pro-calcitonin with high-quality microbiology and this is also complicated by the differentiation between airway ''colonisation'', which is a feature of many chronic lung diseases associated with sputum in the stable state, and ''infection'', in which a clinical deterioration results from the bacteria. In a recent article by FALSEY *et al.* [3], significantly higher pro-calcitonin levels were seen in patients with pneumonia than AECOPD. However, it was concluded that although pro-calcitonin may ''alert clinicians to invasive bacterial infections'', it was poor at distinguishing the varying causes of AECOPD.

Indeed, the major problems of determining the role of bacteria in AECOPD have been the association of bacteria with airway secretions in the stable state and grouping all exacerbations together as if they were a single entity. However, it is accepted that bacteria do play a role in some episodes and clinical trials of antibiotics have shown benefit, supporting this concept [4]. Bacteria are more frequently isolated during acute exacerbations than in the stable state [5]. Nevertheless, differentiating non-bacterial causes remains a major challenge, especially when ''colonisation'' is present in approximately 30–40% of COPD patients in the stable state. However, careful interpretation of the literature and an understanding of pulmonary host defences can present a simplified solution.

Symptoms of an exacerbation of COPD

Defining an exacerbation has been a major intellectual and clinical challenge. First, the patient has to note a change in their clinical status that is recognised to fluctuate from day to day even when the patient is ''well''. Secondly, the symptoms experienced are multiple and include breathlessness, cough, sputum production, chest pain, general lethargy, and nasal and oropharyngeal symptoms. Indeed, this diversity was recognised in defining an acute exacerbation by generalising it as an episode of worsening of symptoms that was both sustained and beyond the normal day-to-day variation requiring a change in therapy [6]. However, that does not mean a bacterial cause and, hence, an indication for antibiotics.

The clue comes from the classical study of ANTHONISEN *et al.* [7], who performed what is still considered to be the gold standard antibiotic trial in AECOPD. These authors noted the three key features of an AECOPD to be increased breathlessness, sputum volume and sputum purulence dividing episodes into three types depending on how many of these features were present. Although the study showed an overall benefit of antibiotic therapy, it was only the Type 1 exacerbations (with all three symptoms) that provided the statistical validity. From this observation, I would draw attention to the single symptom of sputum purulence.

Green sputum

The airways are exposed to 10^4 viable bacteria daily by inhalation and a sophisticated complex of innate host defences exists including airway macrophages, antibacterial proteins and the microbiology escalator. When bacteria overcome this primary defence, replication can occur *in situ* and bacterial numbers increase, stimulating a secondary response that initially involves the recruitment of circulating neutrophils to augment the phagocytic defences and the subsequent activation of the secondary immune system. The ability of the lung to cope with small bacterial loads is best demonstrated in animal models [8]; increasing the load results in bacterial replication and inflammatory cell infiltration.

The same is true in the human lung where neutrophil recruitment and the accompanying inflammation in COPD is bacterial load dependent [9]. Thus, neutrophil infiltration can provide a guide to the influence of local bacterial load. ''Colonisation'' can be defined as a bacterial load that is contained by local defences and ''infection'' when secondary defences are activated and neutrophil recruitment rises. This latter process can be monitored by the assessment of neutrophil-specific proteins such as myeloperoxidase, lipocalin and the granule-specific enzymes. Myeloperoxidase is a 150-kDa dimeric protein stored in the azurophilic granules of the neutrophil. It produces HOCl from H_2O_2 and Cl^- during the respiratory burst but has a haem pigment that gives the cell the characteristic green colour. Thus, the colour of the airway secretions can provide a guide to the neutrophil content [10].

Therefore, the transition from clear or mucoid sputum to an increasingly detectable green colouration provides a watershed between low-grade neutrophilic infiltration (which is a recognised feature of airway inflammation in COPD) and a secondary response to increasing bacterial load. Furthermore, this watershed occurs when the viable bacterial load in sputum from COPD patients reaches and exceeds 10^6 CFU·mL^{-1} [9], which is the same threshold seen in animal studies [8]. For these reasons, the colour alone may provide a simple clinical marker of increased neutrophilic infiltration and, hence, bacterial load and likely ''infection'' in the airways.

The first problem, however, is to standardise colour identification. Although the terms yellow and green are mostly understood, patients are notoriously bad at imparting this information [11]. However, a visual tool for the patient to use in matching colour is reproducible, improves communication and generally relates to colour determination by trained staff (fig. 1). This enables a clear understanding between healthcare workers and patients to occur without receiving or reviewing the specimen.

The use of a matching colour for management of patients with airways infection was first introduced into clinical use for bronchiectasis patients [12], where defining exacerbations and antibiotic prescribing had been largely empirical even within our own tertiary referral clinic.

A formalised colour chart was introduced in the late 1990s for the management and investigation of AECOPD in primary care [13]. At presentation, patients were divided into those with clear or pale sputum and those with dark green sputum. The former group was treated with bronchodilators with or without increased inhaled or oral corticosteroids and the latter group received antibiotics. Both groups improved and patients were able to monitor their sputum colour throughout the resolution period (fig. 2). Of importance, differentiating patients by sputum colour identified those with a high prevalence of bacterial isolation that reduced with resolution of the episode to levels consistent with colonisation whereas those with mucoid samples had no change [13]. Furthermore, evidence of systemic effects, as indicated by C-reactive protein (CRP), was much higher in the green sputum group [13], as was the airway inflammation [14], and this reflected the bacterial load [15]. Following resolution, bacteria were no longer detectable by quantitative culture in some and in others, the quantity fell to levels more consistent with colonisation [15]. Although this was not a formal clinical trial (due to ethical concerns of not treating patients that were preselected by a marker of infection), nevertheless, few patients with

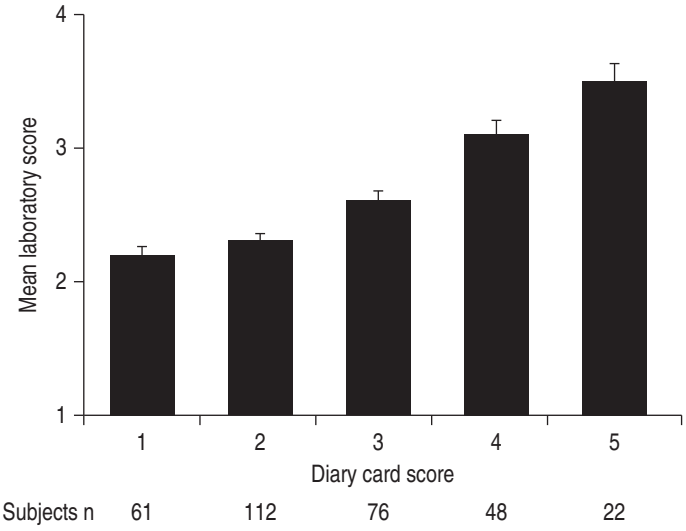

Figure 1. Visual assessment of sputum colour from the daily diary card according to patient *versus* laboratory assessment (by trained laboratory staff) of sputum purulence. Scores of 1 and 2 reflect mucoid sputum and scores of 3–5 represent increasing sputum purulence (green colouration). r=0.516, p<0.001.

mucoid sputum at presentation failed to improve without antibiotics; although, whether the same would have occurred in those with green sputum remains unknown.

The utilisation of this approach has been confirmed by several subsequent studies. A redefined colour chart by JOHNSON *et al.* [16] confirmed that bacterial isolation was low in cream, white or clear sputum and, as such, laboratory costs and antibiotic prescription could be reduced, although clinical outcome was not reported.

In a retrospective meta-analysis, MIRAVITLLES *et al.* [17] again confirmed an association between colour and isolation of the pathogenic bacteria. However, sputum purulence related to the patient description not an objective assessment, although the authors concluded that at least white sputum was a good predictor of negative routine sputum culture. This general observation was subsequently confirmed in patients in the stable state, again using a subjective assessment, to determine the likelihood of colonisation [18].

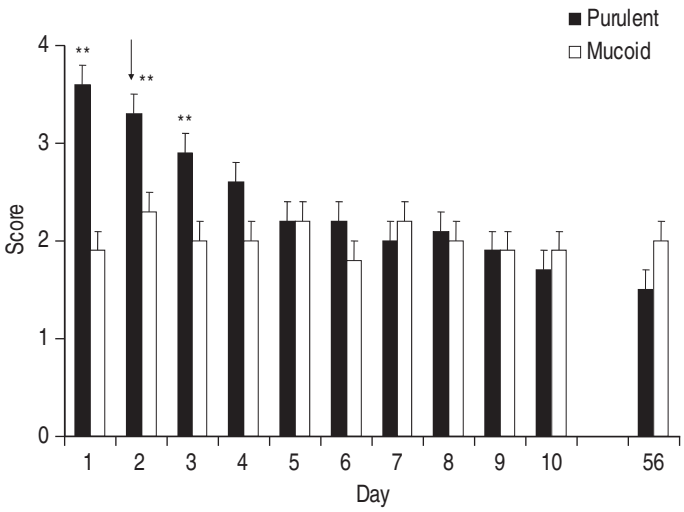

Figure 2. Resolution of sputum colour determined by patients from a colour chart included in a daily diary of the time course of an acute exacerbation of chronic obstructive pulmonary disease following confirmation of whether the presenting sample was mucoid or purulent, as assessed by trained laboratory staff. Data are presented as mean±SE. The arrow represents a significant reduction compared to day 1 (p<0.01). **: p<0.01, significant difference between scores for mucoid and purulent sputum. Data taken from [13].

SOLER *et al.* [19] confirmed that patient-reported purulence predicted distal airway infection (confirmed bronchoscopically) with a sensitivity of 89.5% and specificity of 76.2% during severe exacerbation of COPD. Again, the authors suggested that purulence could help in selecting patients for antibiotic therapy. However, in a large primary care study of all patients presenting with a lower respiratory tract infection, reporting of purulence, although influencing antibiotic prescribing (OR 3.2), did not influence outcome [20]. Unfortunately, again, no objective measures were made and it was a non-COPD population where intact host defences may be sufficient even when bacterial infections are present. Finally, in a more recent paper by SOLER *et al.* [21], of hospitalised patients with AECOPD, antibiotics were restricted to those who subjectively reported the presence of purulent

sputum. There were no differences in short-term outcomes and the use of pro-calcitonin provided no benefit although CRP provided some additional indication of a probable bacterial cause. The results were consistent with those reported by STOCKLEY *et al.* [13] using an objective measure of purulence, and confirm that withholding antibiotics in patients with mucoid sputum at presentation is not detrimental (a practice the author has always used).

To date, the summary of the data indicates that objective characterisation of sputum colour is possible for both patients and healthcare professionals. The presence of mucoid secretions is not associated with an increase in bacterial isolation whereas purulent samples are. In AECOPD, purulent samples are associated with an increased bacterial load, neutrophil content and local and systemic inflammation. Antibiotic therapy can be withheld if sputum is mucoid but direct evidence of antibiotic efficacy in patients presenting with purulent sputum, assessed objectively, is currently lacking.

Patients with chronic purulent sputum production

Chronic purulent sputum production is generally thought to be a feature of a subgroup of patients with CF and non-CF bronchiectasis. Indeed, even in COPD, purulent sputum production in the "stable" state often indicates coexisting bronchiectasis on computed tomography (CT) scans [21]. Such patients have a high sputum bacterial load and extensive neutrophilic infiltration. This provides a conundrum: apparently clinically "stable", patients are showing signs of "infection"; thus, how should it be treated and how is an exacerbation requiring antibiotics defined?

In studies of neutrophilic inflammation in bronchiectasis in the 1980s we were able to demonstrate that not only did appropriate dose and nebulised antibiotics improve sputum colour, but also that patients who had become used to their chronic chest problem noticed an improvement in their wellbeing [22]. These observations are consistent with the association between sputum purulence [9] and sputum bacteria, and bacteria and health-related quality of life [23]. The approach to controlling colonising microbial load has become well entrenched in the management of both CF and non-CF bronchiectasis. Indeed, a recent study by MURRAY *et al.* [24] using pictures of patient sputum in bronchiectasis has not only shown the colour reflects bacterial isolation, but also confirmed the concordance between the patient and doctor that colour reflects the pathological type of the bronchiectasis. The more severe forms of varicose and CF bronchiectasis are associated with gradations in purulent colour. Thus, the most purulent samples reflect the most severe bronchial disruption and bacterial load. At present the cause or effect remains unknown.

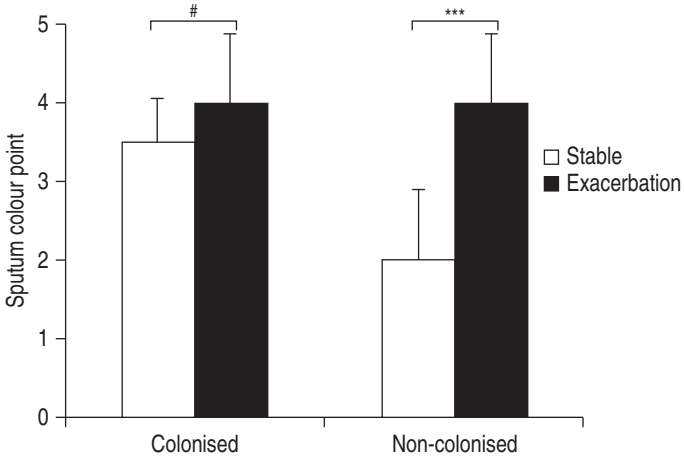

Figure 3. Changes in sputum colour in acute exacerbation of chronic obstructive pulmonary disease (where bacteria were isolated) detected by patients either colonised or not in the stable clinical state. Colour points 1 and 2 reflect mucoid samples and colour points 3–5 increasing sputum purulence. Even patients with purulent sputum in the stable state generally detected an increase in colour at the start of an exacerbation. Data are presented as mean±SE. ***: $p<0.001$; #: $p=0.0015$. Data taken from [13].

Determining deterioration requiring extra antibiotic intervention in such patients becomes more complex. The original paper by ANTHONISEN *et al.* [7] uses the term new or worsening sputum purulence to define an exacerbation. Since sputum colour reflects the colonising bacterial load [9], as the load rises so should the colour

grade and this needs a more accurate objective assessment by the patient and/or treating physician (fig. 3). Thus, even in patients with CF and some with non-CF bronchiectasis, especially those colonised by *Pseudomonas* (which has its own green pigment), the colour often cannot deteriorate further and antibiotic decision making is restricted to more general features such as patient lethargy.

In conclusion, the influence of myeloperoxidase on sputum colour indicates a high or new bacterial load resulting in excessive neutrophil recruitment. An objective assessment of the green colour provides evidence of a change that also reflects a change in bacterial load and, as one of the features of an AECOPD, a prompt for antibiotic therapy. Whereas there is a lack of formal clinical trials in this subgroup, accumulating evidence does suggest that the absence of yellow/green colouration can be used as a guide to withhold antibiotic therapy.

Statement of Interest

None declared.

References

1. Chambers HF. The changing epidemiology of *Staphylococcus aureus. Emerg Infect Dis* 2001; 7: 178–182.
2. Muller B, White JC, Nylen ES, *et al.* Ubiquitous expression of the calcitonin-I gene in multiple tissues in response to sepsis. *J Clin Endocrinol Metab* 2001; 86: 396–404.
3. Falsey AR, Becker KL, Swinburne AJ, *et al.* Utility of serum procalcitonin values in patients with acute exacerbations of chronic obstructive pulmonary disease: a cautionary note. *Int J COPD* 2012; 7: 127–135.
4. Saint S, Bent S, Vittinghoff E, *et al.* Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-anlaysis. *JAMA* 1995; 273: 957–960.
5. Monson E, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; 152: 1316–1320.
6. Rohde GGU. The role of viruses in chronic bronchitis and exacerbations of COPD. *In:* Blasi F, Miravitlles M, eds. The Spectrum of Bronchial Infection. *Eur Respir Monogr* 2013; 60: 68–75.
7. Anthonisen NR, Manfreda J, Warren CPW, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
8. Onofrio JM, Toews GB, Lipscomb MF, *et al.* Granulocyte-alveolar-macrophage interaction in the pulmonary clearance of *Staphylococcus aureus. Am Rev Respir Dis* 1983; 127: 335–341.
9. Hill AT, Campbell EJ, Hill SL, *et al.* Association between airway bacterial load and markers of inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; 109: 288–295.
10. Stockley RA, Bayley D, Hill SL, *et al.* Assessment of airway neutrophils by sputum colour: correlation with airways inflammation. *Thorax* 2001; 56: 366–372.
11. Daniels JM, de Graaf CS, Vlaspolder F, *et al.* Sputum colour reported by patients is not a reliable markers of the presence of bacteria in acute exacerbations of chronic obstructive pulmonary disease. *Clin Microbiol Infect* 2010; 16: 583–588.
12. Stockley RA, Hill SL, Burnett D. Nebulised amoxicillin in chronic purulent bronchiectasis. *Clin Ther* 1985; 7: 593–599.
13. Stockley RA, O'Brien C, Pye A, *et al.* Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; 117: 1638–1645.
14. Gompertz S, O'Brien C, Bayley DL, *et al.* Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. *Eur Respir J* 2001; 17: 1112–1119.
15. White AJ, Gompertz S, Bayley DL, *et al.* Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58: 680–685.
16. Johnson AL, Hampson DF, Hampson NB. Sputum color: potential implications for clinical practice. *Respir Care* 2008; 53: 450–454.
17. Miravitlles M, Marin A, Monson E, *et al.* Colour of sputum is a marker for bacterial colonisation in chronic obstructive pulmonary disease. *Respir Res* 2005; 11: 58.
18. Miravitlles M, Kruesmann F, Haverstock D, *et al.* Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012; 39: 1354–1360.
19. Soler N, Agusti C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 2007; 62: 29–35.
20. Butler CC, Kelly MJ, Hood K, *et al.* Antibiotic prescribing for discoloured sputum in acute cough/lower respiratory tract infection. *Eur Respir J* 2011; 38: 119–125.

21. Soler N, Esperatti M, Ewig S, *et al.* Sputum purulence-guided antibiotic use in hospitalised patients with exacerbations of COPD. *Eur Respir J* 2012; 40: 1344–1353.
22. Hill SL, Burnett D, Hewetson KA, *et al.* The response of patients with purulent bronchiectasis to antibiotics for four months. *Quart J Med* 1988; 66: 163–172.
23. Wilson CB, Jones PW, O'Leary CJ, *et al.* Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J* 1997; 10: 1754–1760.
24. Murray MP, Pentland JL, Turnbull K, *et al.* Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009; 34: 361–364.

Chapter 4

Chronic bronchial infection/colonisation: aetiology and mechanisms

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SUMMARY: Chronic lung diseases that have prominent airway pathology accompanied by a change in the microbial flora of the lung include cystic fibrosis (CF), non-CF associated bronchiectasis, diffuse panbronchiolitis and chronic obstructive pulmonary disease (COPD). The presence of microbial pathogens in the lower airway has been demonstrated in several different ways to have damaging effects in these diseases, and is not innocuous colonisation. Bacterial and host mechanisms contribute to the pathogenesis of this chronic infection, especially disruption in innate lung defence. Several such defects in innate lung defence have been recently described in COPD, including impairment of mucociliary clearance and macrophage function, as well as deficiencies in immunoglobulin A and antimicrobial peptides. Important bacterial persistence mechanisms include host cell invasion, biofilm formation and antigenic alteration.

KEYWORDS: Airway infection, bronchiectasis, *Haemophilus influenzae*, innate immunity, mucociliary clearance, *Pseudomonas aeruginosa*

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Eur Respir Monogr 2013; 60: 34–45.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017212
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The transition from the upper airway (above the glottis) to the lower airway (below the glottis) is accompanied by a dramatic change in normal microbial flora. Whereas very large concentrations of bacteria are present on the mucosa of the upper airway, the lower airways are often sterile by culture methods when carefully sampled by techniques that avoid upper airway contamination [1]. In a recent study, CHARLSON *et al.* [2] used nonculture-based molecular determination of the microbiome of the lower airway in healthy individuals. Even with these sensitive detection techniques, the authors found that there were very low levels of bacterial flora, which resembled the upper airway flora and were most likely transitional flora resulting from normal recurrent microaspiration of upper airway secretions [2].

Colonisation and infection by a pathogen are mainly distinguished by their impact on the host. If the presence of the pathogen elicits damaging effects on the host, which is often accompanied by a

specific host immune response to the pathogen, then that pathogen is regarded as causing an ''infection'' rather than ''colonisation''. Certain chronic lung diseases that have prominent airway pathology are accompanied by a change in the microbial flora of the lung. Best described among these are cystic fibrosis (CF) and non-CF associated bronchiectasis. In both these disorders there is abundant microbial flora in the lower airway, accompanied by exuberant inflammation. There is clear evidence in these disorders that this microbial presence in the lower airway is a chronic infection, which contributes substantially to the chronic phase and acute exacerbations of these disorders. In contrast, until recently, the presence of microbial pathogens in the lower airway in stable chronic obstructive pulmonary disease (COPD) was regarded to be innocuous and as colonisation [3, 4]. The semantics were probably based on the need to distinguish such microbial presence from the infection seen at the time of exacerbation. Recently, several lines of evidence have questioned the validity of this concept and supported the possibility that a proportion of COPD patients may have chronic bronchial infection that contributes to the development and progression of the disease [5].

Vicious-circle hypothesis

The concept that infection and inflammation create a vicious circle was initially espoused for bronchiectasis and later adapted to COPD (fig. 1). This concept has also evolved over time [4–6]. In the context of bronchiectasis, disruption of mucociliary clearance is regarded as the primary driver of the vicious circle [7]. Such impaired mucociliary clearance results in pooling of secretions, thus allowing chronic infection of the airways, which in turn can further worsen mucociliary clearance, thereby setting up the vicious circle. In COPD, the situation is likely to differ and be more complex. Although impaired mucociliary clearance is seen in COPD and contributes to the development of chronic infection, inhalation of noxious particles or gases, *e.g.* tobacco smoke, probably induces several other impairments of innate lung defence. COPD is a heterogeneous disease and it is likely that because of genetic and environmental factors, the extent

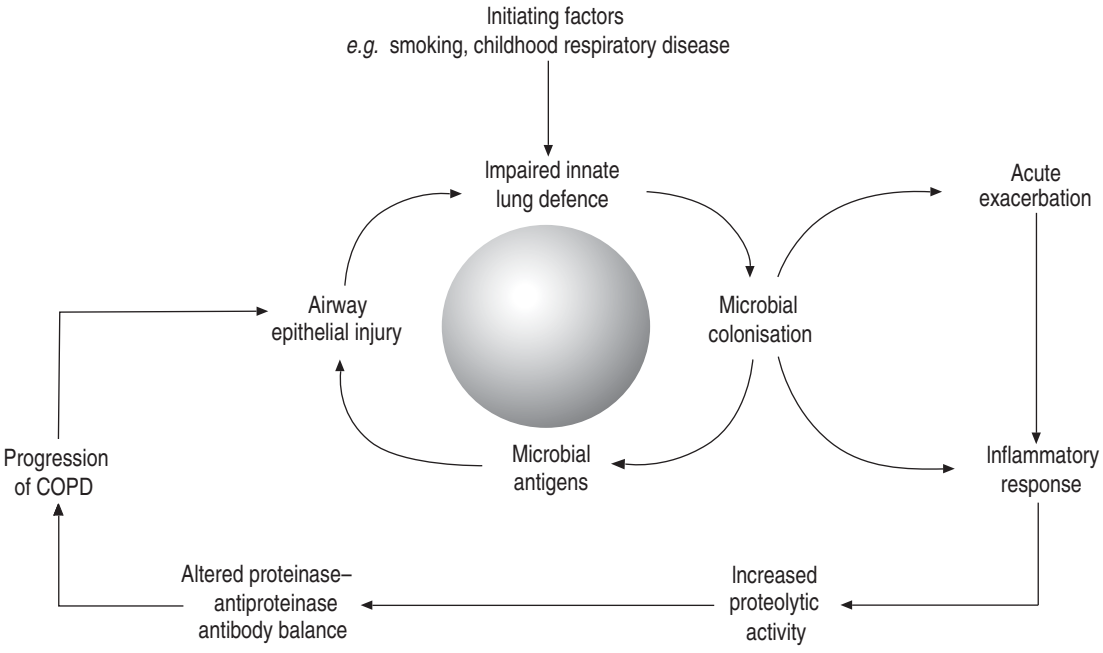

Figure 1. The vicious-cycle hypothesis of infection and inflammation in chronic obstructive pulmonary disease (COPD). After the initial insult impairs innate lung defence, bacterial colonisation perpetuates a cyclical sequence of events that contributes to the persistent inflammation and infection that are characteristic of COPD. Reproduced from [5] with permission from the publisher.

of impaired lung defences varies widely among individuals with COPD. This impairment permits chronic infection, which then induces chronic inflammation, that further disrupts innate lung defence and the vicious circle gets established.

There are two potential mechanisms by which chronic microbial infection could contribute to the pathogenesis of COPD. The microbial pathogen could serve as a primary inflammatory stimulus. Pathogen recognition receptors, such as Toll-like receptors, interact with specific components of microbial pathogens and engender an inflammatory response [8]. Such a mechanism is probably important in chronic colonisation with typical bacteria, such as nontypeable *Haemophilus influenzae* (NTHi) and *Pseudomonas aeruginosa*.

A second potential mechanism by which chronic microbial infection could cause chronic inflammation in COPD is an indirect mechanism. Again, disruption of innate lung defence and failure to clear microbial pathogens is the primary event. The microbial pathogens could then alter the host response to tobacco smoke and potentiate its inflammatory and damaging aspects. Such a mechanism has been described for the adenovirus in COPD, where integration of viral DNA into lung cells appears to enhance the host inflammatory response to tobacco smoke [9].

Evidence for chronic microbial infection in COPD

In order for the chronic microbial presence to be addressed as infection rather than colonisation, evidence for damaging effects to the host and specific immune responses to the pathogens need to be determined. Pathological, radiological and biological evidence of such nature has emerged in the past decade.

In a pathological study by HOGG *et al.* [10], in which pathological features in small airways of COPD at different stages of the disease were examined, the strongest correlate of worsening airflow obstruction was the development of lymphoid aggregates predominantly composed of B-cells. Although alternative explanations, such as autoimmune reactions, could explain this finding, a very likely explanation is that these aggregates represent a local host immune response to deal to chronic microbial infection. Furthermore, in a mouse model of chronic inflammation in the lungs induced by repeated instillation of bacterial lysate (NTHi), the development of very similar looking lymphoid aggregates was a prominent pathological feature [11].

Bronchiectasis and COPD were regarded as distinct diseases, with the former being driven primarily by infection and the latter by inflammation. With the availability and widespread use of high-resolution computed tomography (HRCT) scans in patient with COPD, there is now abundant evidence that bronchiectasis develops in a substantial proportion of patients with COPD. MARTINEZ-GARCIA *et al.* [12] performed HRCT on 92 patients with stable moderate or severe COPD and found that 57.5% had bronchiectasis with a predominantly cylindrical pattern, although cystic changes were also seen. In a multivariate analysis, presence of bronchiectasis in this study was related to worse lung function, a greater likelihood of hospital admission in the past year and chronic bronchitis symptoms. The link of this radiological bronchiectasis to infection was demonstrated by repeated sputum sampling for cultures, which revealed a clear link between chronic colonisation with potential bacterial pathogens (predominantly NTHi and *P. aeruginosa*) and the presence of bronchiectasis [12]. Patients with bronchiectasis also had higher levels of serum fibrinogen and lower levels of serum albumin, probably reflecting chronic inflammation.

Whether colonisation of the lower airway in stable COPD can induce chronic inflammation is essential to support the vicious-circle hypothesis. Several studies utilising sputum or bronchoalveolar lavage (BAL) to measure both infection and inflammation in stable COPD have now been published. We performed a bronchoscopic sampling study in 26 ex-smokers with stable COPD and compared them with 20 ex-smoker non-COPD controls, as well as 15 nonsmoker healthy controls [1]. With careful attention to avoid upper airway contamination, potential bacterial pathogens were detected by culture of BAL samples in 36% of the COPD patients, none of the ex-smokers with COPD and in one of the healthy controls [1]. Furthermore, although

several inflammatory cells and mediators were elevated in COPD, bacterial presence was associated with even greater and statistically significant increases in absolute and relative neutrophil counts, and interleukin (IL)-8 and active matrix metalloproteinase (MMP)-9 levels among the COPD patients [1]. Similar findings were described by SOLER *et al.* [13], and they also found a significant frequency of bacterial presence in the lower airways in smokers with normal lung function.

In another study, in which the authors examined longitudinally obtained sputum samples from a cohort of COPD patients, the impact of acquisition of *Moraxella catarrhalis* on the airway protease (neutrophil elastase activity) and anti-protease (secretory leukocyte protease inhibitor (SLPI)) balance in sputum was determined [14]. Bacterial acquisition, even without an increase in symptoms of an exacerbation, was associated with increases in proteolytic activity and a reduction in anti-proteolytic defence, resulting in worsening of the protease/anti-protease imbalance, which is thought to cause progressive lung damage in COPD. Other similar investigations have shown that bacterial colonisation in stable COPD is associated with other measures of airway inflammation and that the level of inflammation correlates with bacterial concentrations or "load" [15].

Putting together these various lines of investigation supports the paradigm of a vicious circle of infection and inflammation in COPD. It appears that the normal sterility of the lower airway is disrupted, even in smokers who have as yet not developed COPD, and that bacterial presence in this stage of the disease is pro-inflammatory. As COPD develops and progresses, infection gets more frequent and inflammation progresses, lymphoid aggregates develop in the airways and bronchiectatic changes are manifested. However, one must be aware that most of these studies are cross-sectional and show associations. Longitudinal natural history studies or studies with interventions that decrease bacterial colonisation and reduce disease progression would be necessary to firmly prove the vicious-circle hypothesis. COPD is a heterogeneous disease and it would indeed be a surprise if microbial-induced inflammation was implicated in disease pathogenesis to the same extent uniformly among patients with this disease. The proportion of patients for which chronic infection indeed plays a role is probably between 30% and 50%, based on the rate of chronic colonisation, bronchiectasis and bronchitis in this population.

Aetiology of chronic microbial infection

Bacteria

Table 1 shows a list of pathogens that are most often regarded as pathogenic in COPD, based on sputum culture studies. It appears that of these pathogens there are some that may play a more significant role as chronic pathogens. Among the bacterial pathogens, NTHi is the pathogen cultured from lower respiratory tract secretions most frequently in COPD. Furthermore, when we examined sputum samples with microbial detection methods there were several instances when NTHi is detected only by such methods but not by culture. BANDI *et al.* [16] demonstrated NTHi by fluorescent staining with a monoclonal antibody in one-third of bronchial biopsies obtained from patients with stable COPD. MOLLER *et al.* [17] demonstrated that, in lung explants obtained from patients undergoing lung transplant, NTHi was diffusely present in lung tissue by *in situ* hybridisation and PCR.

Therefore, the incidence of chronic infection with NTHi in COPD may be much greater than estimated by culture studies. Chronic NTHi infection has been demonstrated to be associated with chronic inflammation and bronchiectasis in COPD [18]. As discussed below, NTHi has several mechanisms that could allow it to persist in the airways in COPD. The role that NTHi plays in COPD may not be too different from that of *P. aeruginosa* in CF, in being the major pathogen and a major driver of the disease in a significant proportion of patients.

P. aeruginosa becomes prevalent in more advanced stages of COPD. However, its behaviour in COPD does differ from CF, as many of the strains are cleared and the majority are non-mucoid

Table 1. Microbial pathogens implicated in acute and chronic infections in chronic obstructive pulmonary disease

Typical bacteria	Atypical bacteria	Viruses	Fungi
Nontypeable *Haemophilus influenzae*	***Chlamydia pneumoniae***	Influenza	***Pneumocystis jirovecii***
Streptococcus pneumoniae	*Mycoplasma pneumoniae*	Parainfluenza	
Moraxella catarrhalis		Rhinovirus	
Pseudomonas aeruginosa		**Adenovirus**	
Staphylococcus aureus		**RSV**	
Enterobacteriaceae			

RSV: respiratory syncytial virus. Bold denotes pathogens that have been investigated in chronic infection.

[19, 20]. However, both non-mucoid, and especially, mucoid strains can persist in COPD airways for prolonged periods. Chronic infection with *P. aeruginosa* has been linked to bronchiectasis in COPD [12]. Therefore, chronic infection with this pathogen is probably important in advanced COPD.

M. catarrhalis and *Streptococcus pneumoniae* are important causes of exacerbations of COPD. In our longitudinal study, persistence of strains of these pathogens for prolonged periods of time was infrequent [21]. Therefore, their role in chronic infection may be limited. The importance of *Enterobacteriaceae* and *Staphylococcus aureus* as acute and chronic pathogens in COPD is still not fully defined. Nonculture-based detection techniques have revealed an abundance of anaerobic bacteria in CF [22]. The same may be true for COPD but properly conducted studies are still in progress.

As we move to more systematic microbiome-based techniques to assess microbial flora on the airway mucosal surface and in lung tissue, we may find that the aetiology of chronic infection of the bronchi is rather complex. Instead of single pathogens, communities of pathogens that tend to exist together may be implicated in chronic infection. We may also discover microbiomes that are less pro-inflammatory and, therefore, less harmful to the lung.

Virus

There has been considerable interest in the past about adenoviral DNA integration into human lung DNA in COPD, which was then associated with exaggerated inflammation and worse disease [9]. Subsequent studies have not been able to confirm such association [23]. Whether respiratory syncytial virus (RSV) can cause chronic infection in COPD, and thereby contribute to disease progression, is controversial. Recovery of this virus by PCR in stable COPD respiratory samples has been variable among studies [24, 25]. Furthermore, PCR detection methods could be overly sensitive with detection of very low levels of viral presence that are of uncertain pathogenic significance.

Atypical bacteria

The role of chronic *Chlamydophila pneumoniae* infection in COPD remains controversial, despite years of investigation [26]. Earlier studies relying on microimmunofluorescence methods were methodologically flawed [27]. More recent work has used PCR detection of *C. pneumoniae*. There appears to be a greater incidence of pathogen detection in sputum samples as the severity of COPD increases. Von Hertzen *et al.* [28] demonstrated this by PCR and serology in 71% of patients with severe COPD and 46% of mild–moderate COPD compared with 0% in the control group. When such detection methods were applied to excised lung tissue, *C. pneumoniae* was detected in 15% of patients with COPD [29]. However, there was no relationship of such detection and the intensity of inflammation in the lung tissues [29]. Blasi *et al.* [30] have also shown that COPD patients with chronic C. pneumoniae infection have a higher rate of airway microbial colonisation with conventional bacteria than PCR-negative patients and had more frequent exacerbations. Thus, *C. pneumoniae* may act as a co-infection facilitating chronic infection with typical bacteria.

Fungi

Pneumocystis jirovecii is a known pathogen in immunocompromised hosts. In an interesting study, MORRIS *et al.* [31] were able to demonstrate a clear relationship between worse lung function and the detection of this pathogen in lung tissue. Furthermore, HIV-infected patients exhibited greater susceptibility to the development of emphysema on exposure to tobacco smoke [32]. In a primate model, the combination of simian HIV infection and *Pneumocystis* colonisation led to the development of obstructive lung disease [33]. Undoubtedly, these observations increase the interesting possibility of *Pneumocystis* infections contributing to the development of COPD.

Limitations of current knowledge

Although molecular techniques are undoubtedly more sensitive than culture, one has to be aware of their limitations as they: 1) are very prone to contamination and, therefore, false-positive results; and 2) do not provide a microbial isolate for further study, therefore, one cannot confirm the significance of microbial presence by complementary techniques such as immunoassays. Because of their extreme sensitivity, one can question the pathogenetic significance of the presence of a microbial pathogen in very low concentrations and, therefore, the significance of a positive result with these techniques.

Associations, such as those described previously for the typical bacteria and inflammation, are lacking for the other microbial pathogens described as chronic colonisers in COPD. Interestingly, with *Chlamydia, Pneumocystis* and adenovirus the incidence of detection correlates with increasing severity of airflow obstruction in COPD. This could represent a cause–effect relationship; however, an alternative explanation is that increasing airflow obstruction is associated with increasing impairment of innate lung defence, which leads to a greater frequency of colonisation and, therefore, isolation of these pathogens.

Pathogenesis of chronic airway microbial infection

Despite being constantly exposed to a variety of microbes through inhalation and microaspiration, the healthy lung maintains an almost pathogen-free environment. This depends on a multifaceted, redundant and highly efficient innate lung defence system (fig. 2). Therefore, it would be expected that disruptions in this system are necessary to permit chronic infection. Adaptive immune mechanisms, both cellular and humoral, are called into play if innate mechanisms are unable to contain and clear the infection. Dysfunction in these mechanisms could also contribute to persistent infection in COPD, although most studies have shown adequate adaptive response among COPD patients. Microbial pathogens have also evolved mechanisms to evade host immune responses, which undoubtedly could contribute to the establishment of chronic bronchial infection (table 2).

Innate lung defence in COPD

Figure 2 shows the various aspects of innate lung defence. It is likely that several of these mechanisms are disrupted in response to noxious particles or gases, such as tobacco smoke. These could be direct effects of the various compounds in tobacco smoke. In addition, inflammation engendered by tobacco smoke could also have profound effects on innate lung defence. As acute exacerbations and chronic infection become more frequent with increasing severity of COPD, it is likely that perturbations of innate lung defence also become more profound with worsening disease.

Mucociliary clearance

Normal mucociliary clearance, by effectively trapping and clearing inhaled and microaspirated microbial pathogens, is essential to maintain the sterility of the tracheobronchial tree [34, 35].

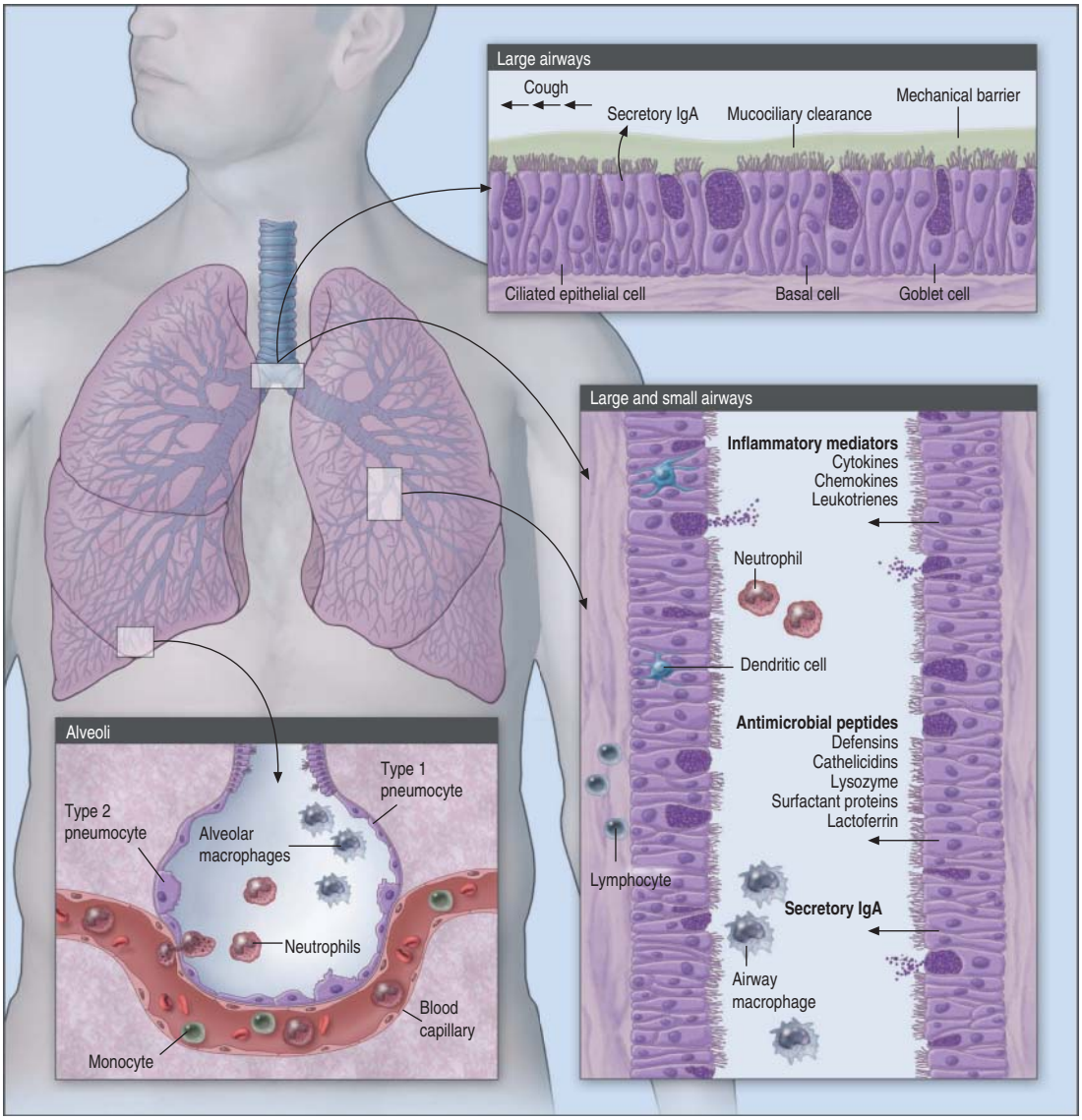

Figure 2. Overview of innate defence in the human respiratory tract. Reproduced from [5] with permission from the publisher. Ig: immunoglobulin.

Disruptions in mucociliary clearance due to alterations in mucus (*e.g.* CF) or mucociliary apparatus (*e.g.* ciliary dyskinesia) are associated with acute and chronic bronchial infection. Smoking disrupts mucociliary clearance by augmenting mucus production and by inducing structural abnormalities in the ciliary apparatus [36]. Impairment of mucociliary clearance is universal, although variable, in moderate-to-heavy smokers, and development of chronic bronchitis and airway obstruction in smokers is associated with further

Table 2. Mechanisms of intermittent and persistent infections in chronic obstructive pulmonary disease

Pathogen	Host
Intracellular persistence	Ineffective innate immunity
Biofilm formation	Ineffective adaptive immunity
Phase variation of surface molecules	
Molecular mimicry	
Mucin binding	
Mucoid phenotype	

deterioration in mucociliary clearance [35, 37, 38]. Neutrophilic inflammation probably contributes to mucociliary impairment, mediated by increased mucus production, reduced ciliary beating and altered viscoelastic properties of mucus.

Immunoglobulin A

IgA is the most abundant immunoglobulin in the lung and 50–70% of this is polymeric secretory IgA. Although IgA is part of the humoral adaptive immune response, it is probable that it plays an important role in innate defence as well. The primary role of IgA is coating of the bacterial pathogen, interfering with its ability to adhere and invade the mucosal surface; the ''immune exclusion'' role. Recent research has demonstrated that IgA can neutralise infectious agents and has other actions by which it assists in the elimination of infectious pathogens. A previous study that examined mucosal IgA in severe COPD demonstrated reductions compared with smoking controls [39]. A recent study has clearly demonstrated localised areas of IgA deficiency in the large and small airways in COPD, which was associated with squamous metaplasia, and appears to be mediated by reduced polymeric IgG receptor expression [40]. This receptor is required for trancytosis of the IgA molecule from the basolateral to the apical surface of the epithelial cell.

Antimicrobial peptides

The airway surface liquid is rich in antimicrobial polypeptides. In addition to their antimicrobial activity, several of these molecules also have important immunoregulatory functions. One major group of these peptides is cationic polypeptides, which include lysozyme, lactoferrin, defensins, cathelicidins (LL-37) and SLPI [41–46]. Susceptibility to exacerbations has been linked with lower levels of salivary lysozyme and sputum SLPI [47, 48]. Dynamic changes in antimicrobial peptides have also been described with bacterial exacerbations of COPD. SLPI levels drop significantly at the time of such exacerbations, returning to baseline after resolution [42]. Lysozyme and lactoferrin levels decrease while LL-37 levels increase with both colonisation and infective exacerbations with NTHi and *M. catarrhalis* [42].

Another important group of antimicrobial polypeptides are the collectins. Surfactant protein (SP)-A and SP-D are collectins with broad-spectrum antimicrobial activity, which also promote phagocytosis by alveolar macrophages [49]. Smokers exhibit lower airway concentrations of SP-A and SP-D, with further decreases in association with emphysema [50, 51]. Another collectin of interest is mannose-binding lectin, with exacerbation frequency in COPD being associated with decreased serum levels [52].

Impaired macrophage function

Alveolar macrophages, along with airway epithelial cells, are key players in the innate cytokine response to invading pathogens. In addition, phagocytosis of bacterial pathogens by alveolar macrophages is vital in dealing with small inocula of pathogens without invoking inflammatory and adaptive immune responses. Alveolar macrophages from COPD patients are less able to phagocytose NTHi and other bacterial pathogens, and have a less robust cytokine response to bacterial proteins, specifically OMP6 and lipooligosaccharide of NTHi [53–55]. Both disease and cigarette smoke exposure contribute to this relative hyporesponsiveness, as alveolar macrophages from ex-smokers have better phagocytic ability than those who continue to smoke; however, both were reduced relative to healthy controls [53, 56].

Several mechanisms could underlie these decrements in macrophage function including reduction in pattern-recognition receptors, such as Toll-like receptors TLR2 and TLR4, reduction in scavenger receptors such as MARCO (macrophage receptor with a collagenous structure) or alteration in subpopulations of macrophages in the airway [57–59]. These alterations may represent down-regulation in an attempt to curb detrimental inflammatory processes in response to tobacco smoke, but may contribute to bacterial persistence and chronic infection as an unintended consequence.

Pathogen mechanisms to sustain chronic airway infection

Not all pathogens are equally represented in acute and chronic infection in COPD. Among the bacterial pathogens there is a disproportionate role of NTHi and *P. aeruginosa* as a cause of chronic

infection in several airway diseases. In contrast, pathogens such as *M. catarrhalis* and *S. pneumoniae* appear much less capable of persistence in the airway but are important causes of acute exacerbation. Pathogen-based mechanisms that could contribute to persistence are listed in table 2.

Tissue invasion

NTHi has been traditionally regarded as an extracellular pathogen. However, several studies have now shown that NTHi can invade and persist in tissues and cells. Nonculture-based molecular detection techniques have demonstrated NTHi in COPD in the bronchial epithelium and inside sub-epithelial macrophages [16, 60]. These tissue bacteria could be more resistant to eradication with antibiotics and antibodies. Furthermore, tissue invasion could explain the ''gaps'' in colonisation seen with NTHi, when the same strain would not be detected by culture on repeat sputum sampling, but could be detected by sensitive molecular-based (PCR) techniques.

Biofilm formation

The classic example of biofilm formation as a mechanism of persistence is with *P. aeruginosa* in CF. Pathogens in biofilm are encased with an extracellular matrix. Furthermore, several of them are less active metabolically. Therefore, they are much less accessible and susceptible to antibiotics and antibodies. As seen in CF, strains of *P. aeruginosa* can persist in the patients for years despite abundant antibodies and repeated exposure to antibiotics. Biofilm formation in the bronchial tree probably contributes substantially to this phenomenon. Whether NTHi and *P. aeruginosa* form biofilms in COPD as they do in CF is not known [61]. Interestingly, mucoid *P. aeruginosa* behave in a similar manner in COPD patients as they do in CF, *i.e.* long periods of persistence in spite of repeated antibiotic exposure.

Antigenic alteration

Another well-described mechanism of persistence for *P. aeruginosa* in CF is changes in surface expression of antigens over time, which helps it evade the host adaptive immune response. A similar phenomenon has been described with persistent isolates of NTHi isolated in COPD, for which a diminution in high-molecular weight adhesin expression has been demonstrated.

Inhaled corticosteroids and chronic bronchial infection

Inhaled corticosteroids (ICS) are widely used in the treatment of COPD, especially in severe and very severe disease. Their anti-inflammatory effects are clearly of benefit, as they reduce symptoms, exacerbations and airflow obstruction, especially when combined with a long-acting β-agonist. However, the immunosuppressive actions of ICS can be a concern in the setting of chronic bronchial infection in COPD. Studies have not been performed to determine the direct effect of ICS on chronic bronchial infection in COPD. However, an indirect effect is seen. In recent years, an increased incidence of pneumonia has been related to the use of these drugs in COPD, primarily with fluticasone use [62, 63]. A dose–response relationship between ICS dose and pneumonia has been seen in many studies, supporting the validity of this observation. Reduction in bronchial lumen and tissue lymphocytes has been observed with ICS use, and could represent the underlying mechanism for the increased incidence of pneumonia [64].

Although pneumonia occurs more frequently in COPD patients treated with ICS, an increase in mortality with ICS use has not been observed. This relative contradiction may be explained by the dampening of the host inflammatory response at the time of pneumonia by ICS use, with a corresponding reduction in severity of illness. More research is needed to evaluate whether the use of ICS needs to be altered in COPD with chronic bronchial infection.

Conclusion

There is undoubtedly increasing recognition of the importance of bronchial infection in several lung diseases. While it was well recognised that bronchial infection drives the disease in CF and

bronchiectasis, its role in COPD is coming under increased scrutiny. It is likely that in a subgroup of COPD patients, chronic bronchial infection contributes substantially to the development and progression of the disease. Compromise of innate lung defence appears to be central to the development of chronic bronchial infection. Pathogens such as NTHi and *P. aeruginosa* have developed mechanisms of persistence that allow them to exploit the compromised airway and cause persistent bronchial infection. Much still needs to be learnt about the impact and mechanisms of chronic bronchial infection. Such understanding could lead to new therapeutics that treat these diseases from a unique perspective.

Statement of Interest

None declared.

References

1. Sethi S, Maloney J, Grove L, *et al.* Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 991–998.
2. Charlson ES, Bittinger K, Haas AR, *et al.* Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med* 2011; 184: 957–963.
3. Tager I, Speizer FE. Role of infection in chronic bronchitis. *N Engl J Med* 1975; 292: 563–571.
4. Murphy TF, Sethi S. Bacterial infection in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1992; 146: 1067–1083.
5. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355–2365.
6. Sethi S. Infection as a comorbidity of COPD. *Eur Respir J* 2010; 35: 1209–1215.
7. Cole P. Host-microbe relationships in chronic respiratory infection. *Respiration* 1989; 55: 5–8.
8. Shuto T, Xu H, Wang B, *et al.* Activation of NF-kappa B by nontypeable *Haemophilus influenzae* is mediated by toll-like receptor 2-TAK1-dependent NIK-IKK α/β-I kappa B α and MKK3/6-p38 MAP kinase signaling pathways in epithelial cells. *Proc Natl Acad Sci USA* 2001; 98: 8774–8779.
9. Hogg JC. Role of latent viral infections in chronic obstructive pulmonary disease and asthma. *Am J Respir Crit Care Med* 2001; 164: S71–S75.
10. Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 2645–2653.
11. Moghaddam SJ, Clement CG, De la Garza MM, *et al. Haemophilus influenzae* lysate induces aspects of the chronic obstructive pulmonary disease phenotype. *Am J Respir Cell Mol Biol* 2008; 38: 629–638.
12. Martinez-Garcia MA, Soler-Cataluna JJ, Donat-Sanz Y, *et al.* Factors associated with bronchiectasis in patients with COPD. *Chest* 2011; 140: 1130–1137.
13. Soler N, Ewig S, Torres A, *et al.* Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. *Eur Respir J* 1999; 14: 1015–1022.
14. Parameswaran GI, Wrona CT, Murphy TF, *et al. Moraxella catarrhalis* acquisition, airway inflammation and protease-antiprotease balance in chronic obstructive pulmonary disease. *BMC Infect Dis* 2009; 9: 178.
15. Hill AT, Campbell EJ, Hill SL, *et al.* Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; 109: 288–295.
16. Bandi V, Apicella MA, Mason E, *et al.* Nontypeable *Haemophilus influenzae* in the lower respiratory tract of patients with chronic bronchitis. *Am J Respir Crit Care Med* 2001; 164: 2114–2119.
17. Moller LVM, Timens W, van der Bij W, *et al. Haemophilus influenzae* in lung explants of patients with end-stage pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 950–956.
18. Bresser P, Out TA, van Alphen L, *et al.* Airway inflammation in nonobstructive and obstructive chronic bronchitis with chronic *Haemophilus influenzae* airway infection. Comparison with noninfected patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 947–952.
19. Murphy TF, Brauer AL, Eschberger K, *et al. Pseudomonas aeruginosa* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 853–860.
20. Rakhimova E, Wiehlmann L, Brauer AL, *et al. Pseudomonas aeruginosa* population biology in chronic obstructive pulmonary disease. *J Infect Dis* 2009; 200: 1928–1935.
21. Murphy TF, Brauer AL, Grant BJ, *et al. Moraxella catarrhalis* in chronic obstructive pulmonary disease: burden of disease and immune response. *Am J Respir Crit Care Med* 2005; 172: 195–199.
22. Sibley CD, Grinwis ME, Field TR, *et al.* Culture enriched molecular profiling of the cystic fibrosis airway microbiome. *PLoS One* 2011; 6: e22702.
23. McManus TE, Marley AM, Baxter N, *et al.* Acute and latent adenovirus in COPD. *Respir Med* 2007; 101: 2084–2090.
24. Falsey AR, Formica MA, Hennessey PA, *et al.* Detection of respiratory syncytial virus in adults with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 639–643.

25. Wilkinson TM, Donaldson GC, Johnston SL, *et al.* Respiratory syncytial virus, airway inflammation, and FEV1 decline in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 871–876.
26. Papaetis GS, Anastasakou E, Orphanidou D. *Chlamydophila pneumoniae* infection and COPD: more evidence for lack of evidence? *Eur J Intern Med* 2009; 20: 579–585.
27. Hammerschlag MR. *Chlamydia pneumoniae* and the lung. *Eur Respir J* 2000; 16: 1001–1007.
28. Von Hertzen L, Alakarppa H, Koskinen R, *et al. Chlamydia pneumoniae* infection in patients with chronic obstructive pulmonary disease. *Epidemiol Infect* 1997; 118: 155–164.
29. Droemann D, Rupp J, Goldmann T, *et al.* Disparate innate immune responses to persistent and acute *Chlamydia pneumoniae* infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 175: 791–797.
30. Blasi F, Damato S, Cosentini R, *et al. Chlamydia pneumoniae* and chronic bronchitis: association with severity and bacterial clearance following treatment. *Thorax* 2002; 57: 672–676.
31. Morris A, Sciurba FC, Lebedeva IP, *et al.* Association of chronic obstructive pulmonary disease severity and Pneumocystis colonization. *Am J Respir Crit Care Med* 2004; 170: 408–413.
32. Crothers K. Chronic obstructive pulmonary disease in patients who have HIV infection. *Clin Chest Med* 2007; 28: 575–587.
33. Shipley TW, Kling HM, Morris A, *et al.* Persistent pneumocystis colonization leads to the development of chronic obstructive pulmonary disease in a nonhuman primate model of AIDS. *J Infect Dis* 2010; 202: 302–312.
34. Knowles MR, Boucher RC. Mucus clearance as a primary innate defense mechanism for mammalian airways. *J Clin Invest* 2002; 109: 571–577.
35. Wanner A, Salathe M, O'Riordan TG. Mucociliary clearance in the airways. *Am J Respir Crit Care Med* 1996; 154: 1868–1902.
36. Verra F, Escudier E, Lebargy F, *et al.* Ciliary abnormalities in bronchial epithelium of smokers, ex-smokers, and nonsmokers. *Am J Respir Crit Care Med* 1995; 151: 630–634.
37. Smaldone GC, Foster WM, O'Riordan TG, *et al.* Regional impairment of mucociliary clearance in chronic obstructive pulmonary disease. *Chest* 1993; 103: 1390–1396.
38. Vastag E, Matthys H, Zsamboki G, *et al.* Mucociliary clearance in smokers. *Eur J Respir Dis* 1986; 68: 107–113.
39. Pilette C, Godding V, Kiss R, *et al.* Reduced epithelial expression of secretory component in small airways correlates with airflow obstruction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 184–194.
40. Polosukhin VV, Cates JM, Lawson WE, *et al.* Bronchial secretory immunoglobulin a deficiency correlates with airway inflammation and progression of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 184: 317–327.
41. Ganz T. Defensins: antimicrobial peptides of vertebrates. *C R Biol* 2004; 327: 539–549.
42. Parameswaran GI, Sethi S, Murphy TF. Effects of bacterial infection on airway antimicrobial peptides and proteins in chronic obstructive pulmonary disease. *Chest* 2011; 140: 611–617.
43. Tjabringa GS, Rabe KF, Hiemstra PS. The human cathelicidin LL-37: a multifunctional peptide involved in infection and inflammation in the lung. *Pulm Pharmacol Ther* 2005; 18: 321–327.
44. Dajani R, Zhang Y, Taft PJ, *et al.* Lysozyme secretion by submucosal glands protects the airway from bacterial infection. *Am J Respir Cell Mol Biol* 2005; 32: 548–552.
45. Ellison RT 3rd, Giehl TJ. Killing of gram-negative bacteria by lactoferrin and lysozyme. *J Clin Invest* 1991; 88: 1080–1091.
46. Fitch PM, Roghanian A, Howie SE, *et al.* Human neutrophil elastase inhibitors in innate and adaptive immunity. *Biochem Soc Trans* 2006; 34: 279–282.
47. Gompertz S, O'Brien C, Bayley DL, *et al.* Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. *Eur Respir J* 2001; 17: 1112–1119.
48. Taylor DC, Cripps AW, Clancy RL. A possible role for lysozyme in determining acute exacerbation in chronic bronchitis. *Clin Exp Immunol* 1995; 102: 406–416.
49. Crouch EC. Structure, biologic properties, and expression of surfactant protein D (SP-D). *Biochim Biophys Acta* 1998; 1408: 278–289.
50. Betsuyaku T, Kuroki Y, Nagai K, *et al.* Effects of ageing and smoking on SP-A and SP-D levels in bronchoalveolar lavage fluid. *Eur Respir J* 2004; 24: 964–970.
51. Honda Y, Takahashi H, Kuroki Y, *et al.* Decreased contents of surfactant proteins A and D in BAL fluids of healthy smokers. *Chest* 1996; 109: 1006–1009.
52. Yang IA, Seeney SL, Wolter JM, *et al.* Mannose-binding lectin gene polymorphism predicts hospital admissions for COPD infections. *Genes Immun* 2003; 4: 269–274.
53. Hodge S, Hodge G, Ahern J, *et al.* Smoking alters alveolar macrophage recognition and phagocytic ability: implications in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2007; 37: 748–755.
54. Berenson CS, Garlipp MA, Grove LJ, *et al.* Impaired phagocytosis of nontypeable *Haemophilus influenzae* by human alveolar macrophages in chronic obstructive pulmonary disease. *J Infect Dis* 2006; 194: 1375–1384.
55. Berenson CS, Wrona CT, Grove LJ, *et al.* Impaired alveolar macrophage response to *Haemophilus* antigens in chronic obstructive lung disease. *Am J Respir Crit Care Med* 2006; 174: 31–40.
56. Marti-Lliteras P, Regueiro V, Morey P, *et al.* Nontypeable *Haemophilus influenzae* clearance by alveolar macrophages is impaired by exposure to cigarette smoke. *Infect Immun* 2009; 77: 4232–4242.

57. Droemann D, Goldmann T, Tiedje T, *et al.* Toll-like receptor 2 expression is decreased on alveolar macrophages in cigarette smokers and COPD patients. *Respir Res* 2005; 6: 68.
58. Harvey CJ, Thimmulappa RK, Sethi S, *et al.* Targeting Nrf2 signaling improves bacterial clearance by alveolar macrophages in patients with COPD and in a mouse model. *Sci Transl Med* 2011; 3: 78ra32.
59. Kunz LI, Lapperre TS, Snoeck-Stroband JB, *et al.* Smoking status and anti-inflammatory macrophages in bronchoalveolar lavage and induced sputum in COPD. *Respir Res* 2011; 12: 34.
60. Murphy TF, Brauer AL, Schiffmacher AT, *et al.* Persistent colonization by *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 266–272.
61. Starner TD, Zhang N, Kim G, *et al. Haemophilus influenzae* forms biofilms on airway epithelia: implications in cystic fibrosis. *Am J Respir Crit Care Med* 2006; 174: 213–220.
62. Ernst P, Gonzalez AV, Brassard P, *et al.* Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med* 2007; 176: 162–166.
63. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med* 2009; 169: 219–229.
64. Jen R, Rennard SI, Sin DD. Effects of inhaled corticosteroids on airway inflammation in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 587–595.

Chapter 5

Impact of chronic bronchial infection on the lungs and beyond

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SUMMARY: Impaired host defences in chronic bronchial diseases allow the establishment and proliferation of potentially pathogenic microorganisms (PPMs). This is particularly frequent in patients with chronic obstructive pulmonary disease (COPD). Repeated isolation of PPMs in bronchial secretions in stable patients was defined as colonisation; however, it is well documented that the presence of PPMs in the lower airways is associated with increased exacerbation frequency and severity, faster lung function decline and worse health status. Therefore, the term chronic bronchial infection (CBI) has been proposed to define this clinical situation.

The presence of CBI in COPD is characterised by increased chronic inflammation not only in the airways and lung parenchyma, but also at a systemic level. Current evidence indicates that a significant amount of local and systemic inflammatory response in COPD may be attributable to the presence of PPMs. Since atherosclerosis is also characterised by chronic inflammation and oxidative stress, it has been hypothesised that CBI may be responsible for some extra-pulmonary manifestations of COPD, particularly the high prevalence of cardiovascular comorbidities.

KEYWORDS: Chronic obstructive pulmonary disease, colonisation, comorbidities, exacerbation, infection, inflammation

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Eur Respir Monogr 2013; 60: 46–57.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017312
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The bronchial tree of healthy individuals has defence mechanisms that protect the lungs against the proliferation of microorganisms. However, different insults, tobacco smoking being the most frequent, can impair these mechanisms and chronic infection may develop. There is a spectrum of different clinical situations in which chronic bronchial infection (CBI) may take place, among them cystic fibrosis (CF), bronchiectasis and chronic obstructive pulmonary disease (COPD) are the most frequent. The aetiology of CBI is complex and includes the usual respiratory bacteria, atypical bacteria, viruses and even eukaryotic opportunistic pathogens such as *Pneumocystis jiroveci* [1]. Other chapters of this *Monograph* will be dedicated to the impact of

viruses and to specific bronchial diseases such as bronchiectasis, therefore, the focus of this chapter will be on bacterial CBI in patients with COPD.

The threshold between CBI and acute exacerbation in COPD (AECOPD) is not always easy to establish. Most microbiological studies in stable and exacerbated patients with COPD have observed that the microorganisms involved are largely the same [2–7]. The virulence capacity of microorganisms and impairment in the host defences lead to constant changes in the host–pathogen relationship [3, 8, 9]. Microbial variability and exposure to cigarette smoke, together with additional intrinsic and extrinsic factors, determine the nature and intensity of CBI and the associated airway inflammation [10]. Nonetheless, the intensity of bronchial inflammation is predominantly associated with the presence of bacteria and their load in bronchial secretions [11–13]. Periods of enhanced inflammation are associated with functional deterioration and acute worsening of chronic respiratory symptoms, *i.e.* clinical manifestations of exacerbations [14, 15].

Inflammation in COPD is not limited to the lungs; there is a certain level of systemic inflammatory response not only during exacerbations but also in stable periods [16]. There is increasing evidence that CBI, together with exposure to smoking, may be responsible for the permanent inflammation in COPD and accelerate the progression of the disease [17]. Chronic inflammation and oxidative stress are also crucial in the pathogenesis of atherosclerosis and given that cardiovascular and cerebrovascular diseases are frequent comorbidities and causes of death in COPD patients, it has been hypothesised that the presence of microorganisms in the bronchial tree could be the link between these two inflammatory disorders [18].

Chronic bronchial infection in COPD

The concept of CBI in COPD is the result of a revision of the old concept of colonisation, and is characterised by the presence and proliferation of microorganisms in the lower airways and the associated consequences [19, 20]. Microorganisms capable of inducing respiratory infection with significant inflammatory response in the immunocompetent host are categorised as potentially pathogenic microorganisms (PPMs) and include *Haemophilus* spp., *Streptococcus pneumoniae, Moraxella catarrhalis, Staphylococcus aureus, Pseudomonas aeruginosa* and some members of a large Enterobacteriaceae family (*Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Serratia marcescens* and *Enterobacter cloacae*) [2, 21]. However, non-PPMs belong to the normal oropharyngeal and gastrointestinal flora. According to current evidence, their presence on the mucous membranes of immunocompetent individuals is harmless and includes species such as *Candida* spp., *Corynebacterium* spp., *Neisseria* spp., *Enterococcus* spp., coagulase-negative *Staphylococcus* spp. and *Streptococcus viridans* group [21]. Moreover, even in the group of PPMs, different species differ in their pathogenic potential, *e.g. Haemophilus parainfluenzae* and *Haemophilus haemolyticus* induce a much lower level of inflammation in comparison to nontypeable *Haemophilus influenzae* (NTHi) and other PPMs [3, 22, 23]. This is why increasingly more authors have classified *H. parainfluenzae* and *H. haemolyticus* as non-PPMs [16, 23, 24].

The lower airways of healthy nonsmoking individuals are usually sterile, and possible colonisation is mainly by non-PPMs [2, 6, 21, 25]. In COPD and chronic bronchitis, impairment in lung defences, including inefficient mucociliary clearance, facilitates bacterial growth in distal airways [26–28]. Consequently, both PPMs and non-PPMs are frequently recovered from the lower respiratory tract specimens taken from these subjects, both in stable periods and during exacerbations [4–7]. It is of note that the rates of positive cultures vary depending on the sampling technique and cut-off points employed. In bronchoscopic studies with stable COPD patients using protected specimen brush (PSB) to obtain bronchial lavage and/or bronchoalveolar lavage samples, between 20% to 80% of cultures are positive for bacteria, and 25–40% are positive for PPMs [2, 6, 7, 21, 25, 29–31]. Sputum samples are easiest to obtain in COPD patients with chronic cough and expectoration, and their cultures are positive in up to 100%, with PPMs yielded in ~40–70% [3, 4, 8, 12, 32, 33]. Table 1 summarises the prevalence rates of positive sputum cultures and the PPMs most frequently isolated in stable COPD.

Table 1. Positive sputum cultures in stable chronic obstructive pulmonary disease (COPD) and the most frequently isolated pathogens

First author [ref.]	Patients	FEV1 % pred	Specimen/cut-off value for positive culture	Culture positive for any bacteria	Culture positive for PPM	Most frequently isolated PPM
PAPI [5]	Stable, convalescent COPD (8–10 weeks after an exacerbation): n=64	50	Induced sputum, n=64/ $\geqslant 10^6$ CFU·mL^{-1}		24 (38)	*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, *S. aureus*
WILKINSON [8]	Stable COPD: n=30	35	Spontaneously expectorated or induced sputum, n=30/ $>10^5$ CFU·mL^{-1}	30 (100)	At baseline: 16 (53) After 1 year: 17 (57)	*H. influenzae*, *M. catarrhalis*, *H. parainfluenzae*
HILL [12]	Stable chronic bronchitis, n=160:		Spontaneously expectorated sputum, n=336/ $\geqslant 10^5$ CFU·mL^{-1}		247 (74)	*H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *P. aeruginosa*
	COPD, n=55	28				
	COPD with α_1-AT deficiency, n=62	21				
	Bronchiectasis, n=43	62				
MARIN [3]	Stable COPD, n=40	58	Induced sputum, n=79/ $\geqslant 10^2$ CFU·mL^{-1}		At baseline: 58 (73) After 9 months: 56 (71)	*H. influenzae*, *P. aeruginosa*, Enterobacteriaceae, *H. parainfluenzae*
MIRAVITLLES [32]	Stable COPD, n=119	46	Spontaneously expectorated or induced sputum, n=119/ $\geqslant 10^2$ CFU·mL^{-1}		58 (49)	*H. influenzae*, *H. parainfluenzae*, *P. aeruginosa*
PATEL [4]	Stable COPD, n=29	39	Induced sputum, n=29/ not provided		15 (52)	*H. influenzae*, *S. pneumoniae*
BANERJEE [33]	Stable COPD, n=67	~40	Induced sputum, n=67/not provided	67 (100)	27 (40)	*H. influenzae*, *M. catarrhalis*, *S. pneumoniae*

Data are presented as n (%), unless otherwise stated. FEV1: forced expiratory volume in 1 s; % pred: % predicted; CFU: colony forming units; PPM: potentially pathogenic microorganism; α_1-AT: α_1-antitrypsin; *H. influenzae*: nontypeable *Haemophilus influenzae*; *S. pneumoniae: Streptococcus pneumoniae; M. catarrhalis: Moraxella catarrhalis; S. aureus: Staphylococcus aureus*; *H. parainfluenzae: Haemophilus parainfluenzae; P. aeruginosa: Pseudomonas aeruginosa*. Reproduced from [20] with permission from the publisher.

However, when culturing sputum specimens and interpreting the results, some limitations must be considered. Sputum mostly comes from large airways and is often contaminated by upper airway microbial flora thereby lowering the specificity of this method. Furthermore, when bacterial loads are below the detection limit of sputum cultures, they may yield false negative results unlike novel, more sensitive, nonculture-based techniques such as PCR for detection of microbial nucleic acid in respiratory specimens [13, 34]. However, when using good-quality sputum samples, *i.e.* Murray–Washington classification degrees IV or V (degree IV: 10–25 epithelial cells and >25 leukocytes per field; degree V: ⩽10 epithelial cells and >25 leukocytes per field using a low magnification lens (× 100) [35]), sputum cultures have a high sensitivity and 85% correlation with PSB cultures [24], which justifies their broad use in both clinical practice and respiratory research, especially in longitudinal studies in which the use of the more sensitive and specific techniques, such as the bronchial brush and the bronchoalveolar lavage, would be inappropriate. Another advantage of classical microbiological culturing of sputum and other respiratory specimens in comparison with PCR techniques is the usefulness of the simultaneous identification of the antibiotic sensitivity profile of isolated PPMs.

The PPMs most frequently recovered from respiratory specimens in stable COPD include NTHi, *S. pneumoniae, M. catarrhalis* and *H. parainfluenzae* (table 1) [3, 4, 6, 7, 36]. Multibacterial colonisation is not uncommon [6, 12, 33], while *Pseudomonas* spp. are predominately found in patients with more severe functional impairment [12, 25] and those with clinically significant bronchiectasis [25].

In everyday practice, in which sophisticated techniques are not available, some clinical features may help us to recognise COPD patients at the highest risk for CBI with PPMs. A positive smoking history [16, 30, 31], severely impaired lung function [6, 13, 30, 31], comorbidities [32], frequent exacerbations [4, 32], bronchiectasis [25], purulent expectoration [32], increased dyspnoea [32] and inhaled corticosteroid use at high doses [13] have been associated with CBI in COPD.

Finally, the relevance of what has been called the microbiota in lung health must be established. Molecular culture-independent techniques have identified bacteria previously not amenable to culture. Analysis of the highly conserved 16S rRNA gene has been used to assign phylogeny and allows a picture of the complete microbial community in an environment (the bronchial tree) to be constructed, providing a more comprehensive analysis than classical culture-based techniques [37]. The number of studies examining the lower airways microbiome is limited and there is some overlap between the bacteria seen in COPD and healthy individuals [38]; however, a recent study has reported a significantly different bacterial community (microbiome) in patients with very severe COPD compared with healthy nonsmokers, smokers and patients with CF [39]. Further studies are clearly needed to understand the role of these microbiomes in healthy individuals and patients with COPD and how treatments can interfere with the species identified in the lung microbiome.

Impact of chronic bronchial infection on the lungs

Microorganisms may reach the distal airways by inhalation of infective aerosol or microaspiration of respiratory secretions from the upper airways, while the haematogenous spread or aspiration of gastric content would be infrequent mechanisms. In healthy and immunocompetent individuals, pathogenic microorganisms are usually successfully cleared from the airways by the effectiveness of the innate and adaptive immunity [2, 6, 21, 25]. However, COPD patients demonstrate different forms of immune impairment, including reduced mucociliary clearance, defective phagocytosis and hyporesponsiveness of alveolar macrophages to bacterial antigens with the subsequent predisposition to infection [26–28]. Among these mechanisms, airway mucus plays a main role and under normal circumstances it protects the epithelial lining by entrapping harmful particles and clearing them from the airway by ciliary movement in a process called mucociliary clearance [26]. Cigarette smoke, bacterial infection, cold air, different irritants and allergens cause mucus secretion by inducing the release of inflammatory mediators or nerve activation [26, 40]. As an

acute response to the inhaled insult, this process can be considered protective but chronic exposition to the noxious agents leads to mucin genes overexpression, goblet cell hyperplasia and submucosal gland hypertrophy, further leading to mucus hypersecretion, defective mucociliary clearance and airway obstruction [26]. Some bacteria such as NTHi have the ability to bind with their outer membrane proteins to the carbohydrate side-chains of mucin molecules; a process that may facilitate airway colonisation in the condition of mucus hyperproduction [41]. The vicious circle between bacterial infection and mucus hypersecretion is further complicated by the fact that the reduced numbers of serous and club cells (Clara cells), as a consequence of globet cell hyperplasia, result in low concentrations of their protective molecules in respiratory secretions and may additionally explain the increased propensity for bacterial growth in the lower airways of patients with mucus hypersecretion [26, 42].

The virulence capacity of individual pathogens may vary, but generally bacteria have developed a wide range of mechanisms to damage epithelial cells, impair ciliar activity, attach to the mucous membranes or extracellular matrix, and to evade host immune defences [41, 43]. Furthermore, the pathogenic characteristics of the same species may change over time, as has been demonstrated in COPD patients with CBI by *P. aeruginosa*. Their isolates have distinct characteristics similar to those found in patients with CF, *i.e.* the coexistence of isolates with different morphotypes and antibiotic susceptibility, a high prevalence of hypermutable strains, increased biofilm production, reduced production of virulence factors and an increased rate of antibiotic resistance [44].

Bacteria release different proinflammatory molecules such as endotoxins, outer membrane lipoproteins, peptidoglycan fragments, lipoteichoic acid, toxins, *etc.* [45–47]. Driven by these molecules, airway epithelial cells and macrophages produce a variety of inflammatory mediators (*e.g.* interleukin (IL)-1, IL-6, IL-8, IL-10, tumour necrosis factor (TNF)-α, macrophage chemotactic proteins, *etc.*), further leading to the recruitment and activation of different inflammatory cells [46–49]. Neutrophils are recruited from the circulation in response to chemoattractants, particularly IL-8 and leukotriene B4, *via* adhesion molecules expressed on the vascular endothelium. The activated neutrophils degranulate, releasing powerful enzymes (myeloperoxidase and different types of proteinases) capable not only of destroying microorganisms but which may also cause significant lung tissue damage.

In general, infected airways show higher levels of inflammatory cytokines, neutrophils and their products in comparison with airways without PPMs [2, 11]. Differences also arise from the variation in the virulence properties of the different species [12, 50]. Moreover, even different strains of the same species may differ in their inflammatory potential; persisting NTHi strains induce lower levels of inflammatory cytokines than nonpersisting strains [51].

The host–pathogen interaction is a complex and dynamic process, with the balance between host defences and microbial activity being influenced by multiple factors and difficult to establish. As an example, colonisation by *M. catarrhalis* is generally of shorter duration; this pathogen is usually cleared from the airways efficiently in a period of 1 month, even without antibiotics [52]. Conversely, NTHi and *P. aeruginosa* are associated with prolonged or even chronic infection [34, 44, 53].

The acquisition of PPMs induces not only local but also systemic inflammatory response [52]. In the lungs, changes in colonising bacterial type and increase in loads and subsequent enhancement in the level of airway inflammation have been associated with an accelerated decline in forced expiratory volume in 1 second (FEV_1) [8]. Further impact of bacteria on the lung functional impairment can be expected through the increased exacerbation frequency and severity observed in chronically infected patients [4].

There is increasing evidence that PPMs play an important role in the pathogenesis and progression of COPD. The usual term ''colonisation'' suggests passive and harmless coexistence of bacteria on the mucous membranes of an asymptomatic host. Not only are PPMs not passive bystanders but rather, they actively contribute to airway and systemic inflammation with all the subsequent negative consequences. Supported by current evidence, a change in the terminology has recently been suggested favouring the term ''chronic bronchial infection'' when addressing the isolation of a significant load of PPMs in the distal airways in stable COPD patients [17, 19, 20]. The term

colonisation should be reserved for the presence of non-PPMs in the respiratory tract of individuals with or without a chronic respiratory disease. A double vicious circle in the interaction between PPMs and the lungs has been proposed. The acute circle explains the sequence of events occurring during acute exacerbations and the chronic circle represents the events associated with CBI, with both being interrelated (fig. 1) [19].

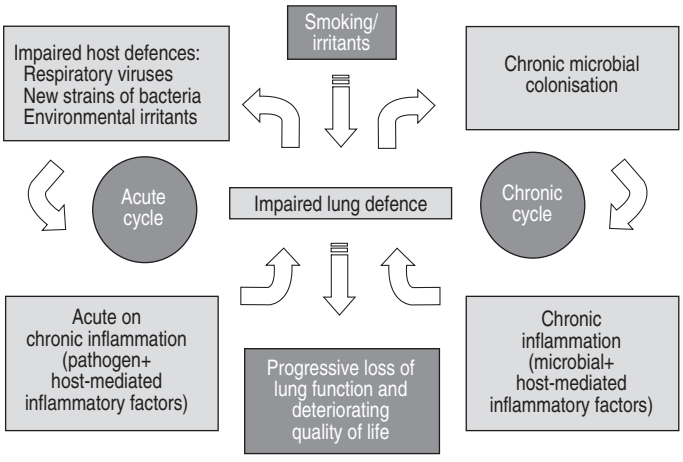

Figure 1. Two distinct infectious cycles in chronic obstructive pulmonary disease: acute and chronic. Reproduced from [19] with permission.

Impact of chronic bronchial infection beyond the lungs

There is no doubt that exacerbations produce an increase in systemic inflammation that is responsible for the impairment in the health status of the patients. Additionally, this systemic impact may be responsible for the increased risk of cardiovascular events during and soon after the exacerbation episodes [54]. The systemic impact of CBI has not been as extensively investigated, although a few studies have described an impaired quality of life associated with the presence of CBI in patients with COPD [33, 55]. A recent study has demonstrated that patients with COPD and positive sputum cultures have significantly higher sputum concentrations of IL-1β, IL-6 and IL-8 compared with patients with negative sputum; furthermore, they also have significantly elevated levels of serum C-reactive protein (CRP) and significantly worse scores in the activity and impact domains of the St George's Respiratory Questionnaire (SGRQ) [16].

More interestingly, a link between CBI in COPD and atherosclerosis has been proposed. Both are chronic, progressive, frequently coexisting disorders that share several risk factors and recognise common pathogenic pathways, such as inflammation and oxidative stress [18]. Smoking is one of the most relevant risk factors for atherosclerosis, but this risk is significantly reduced after cessation of smoking unless there is clinical or serological evidence of chronic airway infection [56]. Some animal studies have also demonstrated that short-lasting infectious insults could cause endothelial dysfunction and arterial damage, thus contributing to atherosclerosis progression [18, 57]. However, there is no single infectious agent implicated in the genesis of atherosclerosis; instead it has been suggested that the infectious burden resulting from numerous infections throughout life are most likely factors associated with the development of atherosclerosis [18]. In this respect, COPD patients with CBI would be the paradigm of the patients at increased risk for cardiovascular and cerebrovascular diseases, which are the most important clinical manifestations of atherosclerosis.

The relationship between chronic and acute bronchial infection

Investigations preformed in recent years have sought to establish the underlying pathophysiological process of exacerbations of COPD. In comparison to the stable state, there is an acute increase in the level of airway inflammation during periods of exacerbations, assessed by a rise in sputum inflammatory cells (neutrophils, eosinophils and lymphocytes) and different inflammatory mediators [5, 48, 50]. Intensified inflammation may induce airway mucosal oedema, bronchospasm and mucus hypersecretion, further leading to increased respiratory symptoms [15]. The association between neutrophilic inflammation, sputum purulence and bacterial exacerbations is well established and provides a rationale for using sputum purulence as a clinical indicator of bacterial infection and the need for antibiotic therapy [58–60].

Published data suggest that up to 70% of exacerbations are caused by respiratory infections including aerobic bacteria (40–60%), respiratory viruses (~30%) and atypical bacteria (5–10%) [61, 62]. Some authors have demonstrated polymicrobial aetiology in as much as 33% of exacerbations, being particularly important in the most severe cases [5, 63]. Exacerbations are the main cause of patients seeking medical attention and the main cause of hospital admission in COPD. Furthermore, a significant number of admitted patients have a poor evolution, including early readmission or even death [64].

Considering bacterial exacerbations, NTHi, *S. pneumoniae* and *M. catarrhalis* are the most frequently isolated PPMs from respiratory secretions during these episodes, similar to what occurs in the stable state [5–7]. Other Gram-negative bacteria, such as *P. aeruginosa, Stenotrophomonas maltophilia* and members of the Enterobacteriaceae family, are more often present in patients with a greater degree of functional impairment, recent antibiotic or systemic steroid therapy, and in those with severe exacerbations [63, 65, 66].

Interestingly, PPMs are more frequently isolated, and with higher loads during exacerbations compared to the stable state. They can be found in ~50% of exacerbated patients when using PSB samples, usually with $>10^7$ CFU·mL^{-1} in sputum cultures and $>10^3$ CFU·mL^{-1} in PSB cultures [5–7]. All these findings and the fact that the severity of bronchial inflammation is directly correlated with bacterial load [12] led to the development of the "fall and rise" or quantitative hypothesis of bacterial exacerbations of COPD [10]. Based on this hypothesis, symptoms of exacerbation appear when the inflammatory reaction caused by the increasing bacterial load in the airways exceeds a certain threshold, which is determined by a combination of bacterial and host factors [10]. However, findings based on molecular typing of bacterial isolates have demonstrated that the acquisition of new strains of bacteria or antigenic change in pre-existing strains are crucial in the pathogenesis of bacterial exacerbations, and that a change in the bacterial load with subsequent enhancement of inflammation are just secondary phenomena [9, 15, 36]. Following a cohort of ambulatory COPD patients over more than 4 years, SETHI *et al.* [9] demonstrated that the acquisition of a new strain of NTHi, *S. pneumoniae* and *M. catarrhalis* was associated with more than a two-fold higher risk for an exacerbation. In a more recent study of a similar design but with a longer follow-up, MURPHY *et al.* [53] have shown that the same association between a change in a strain and the occurrence of exacerbations also exists for *P. aeruginosa*. It has been suggested that after a new strain is acquired due to the absence of an effective host immune response, bacteria may intensively proliferate in the airways resulting in a higher bacterial load, more severe local and systemic inflammation and the development of symptoms of exacerbation [15, 67]. The immune response to the infecting strain, which develops after an exacerbation, is strain-specific and not protective against the acquisition of new strains [52, 68, 69], which may explain recurrent exacerbations even by the same species [70]. Moreover, this specific immune response provides indirect evidence that the particular microorganism was actually the cause of the exacerbation [52, 68, 69]. Both factors, a change in the infecting strain and an increase in bacterial load, have been demonstrated to be related to the development of an exacerbation. To increase the complexity of the pathogenesis of bacterial exacerbations, a human experimental model has demonstrated that a viral infection by rhinovirus is followed by secondary bacterial infections in subjects with COPD but not in smokers or nonsmokers without COPD. These infections produce the same sequence of events as a naturally occurring exacerbation of COPD [71]. Up to now, no single mechanism can fully explain the pathogenesis of bacterial exacerbations of COPD.

Infectious phenotype of COPD

In view of the above, it is clear that the isolation of PPMs from respiratory samples does not fulfil the definition of colonisation, since it is associated with an inflammatory response and significant damage to the target organ. This is why it has recently been suggested that the term CBI would be more appropriate when addressing the presence of significant concentrations of PPMs in the lower airways of stable COPD patients [17, 19, 20]. CBI in COPD can be defined as the presence of

PPMs in respiratory secretions that cause an inflammatory reaction manifested by the chronic production of coloured/purulent sputum. This syndrome can be accompanied by recurrent infective exacerbations and systemic manifestations in the form of malaise, febricula, asthenia or weight loss, similar to what has been described in patients with bronchiectasis (fig. 2). In fact, most of these patients have significant bronchiectasis when studied by high-resolution computed tomography (CT) scan. In the study by MARTINEZ-GARCÍA *et al.* [72], the isolation of a PPM in sputum in a patient with stable COPD, together with an FEV1<50% predicted and the history of

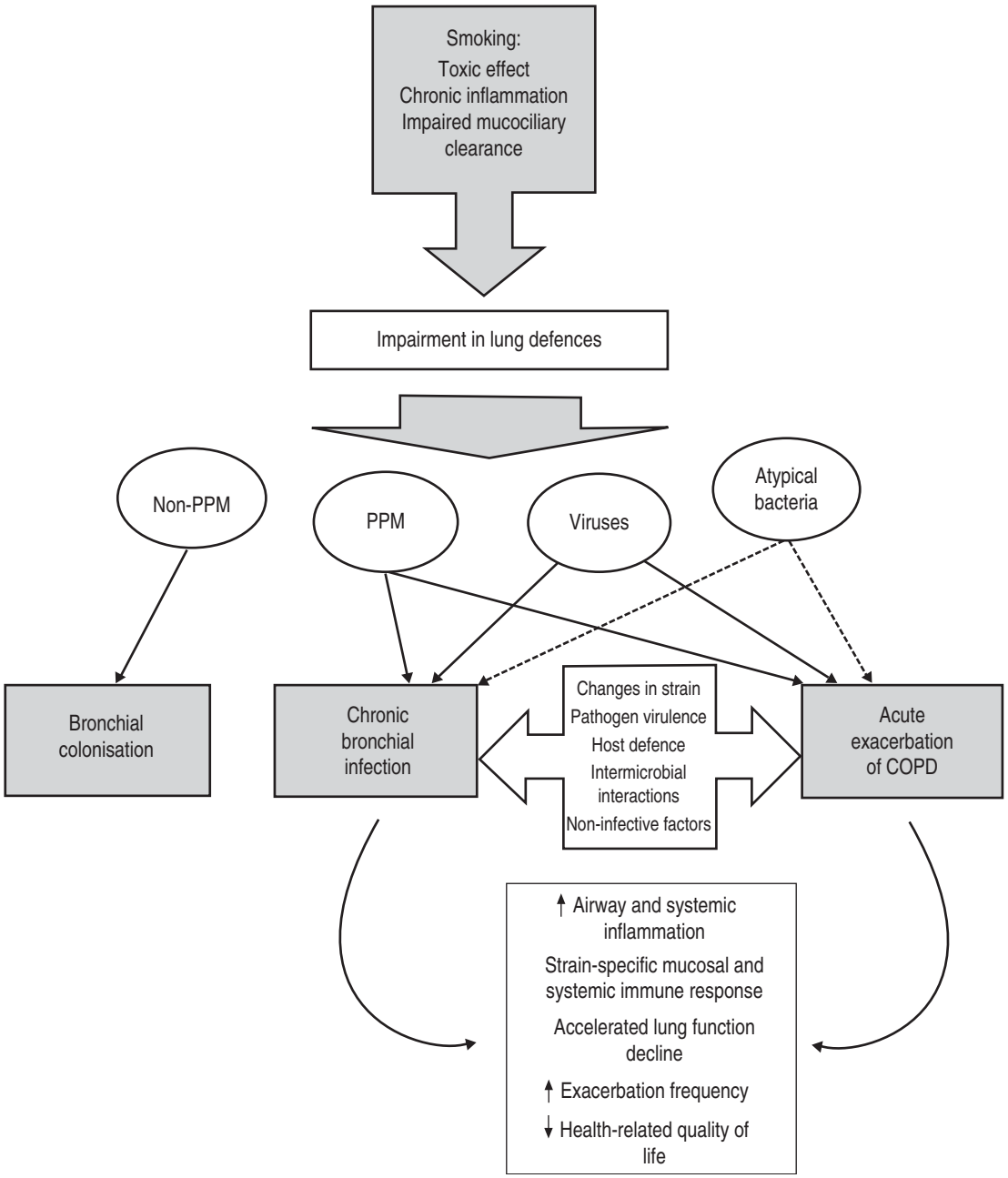

Figure 2. The impact of microbial infection on the pathogenesis of chronic obstructive pulmonary disease (COPD) in both the stable state and during exacerbations. Since the current evidence for the role of atypical bacteria is incomplete, they are presented with a dashed line. PPM: potentially pathogenic microorganism. Reproduced from [20] with permission from the publisher.

at least one hospital admission for an exacerbation the previous year were associated with a 99% probability of having bronchiectasis on CT scan.

Besides common bacteria, respiratory viruses and atypical bacteria in the form of chronic infection may also have an impact on the course of COPD [73–75]. SEEMUNGAL *et al.* [73] analysed nasal aspirates and blood samples of stable COPD patients by PCR and detected low-grade viral infection with respiratory syncytial virus (RSV) in 24% of patients, as well as infection with viruses other than RSV (predominantly rhinoviruses and coronaviruses) in 16% of patients. Patients in whom a virus was detected were more likely to have increased exacerbation frequency as well as higher concentrations of serum IL-6 and plasma fibrinogen (potential predisposition to thrombotic events) when stable [73]. Furthermore, on examining the lung tissue of smokers with different degrees of emphysema, RETAMALES *et al.* [74] determined a 5- to 40-fold increase in the number of alveolar epithelial cells expressing adenoviral E1A protein in mild and severe emphysema, respectively, and suggested the impact of latent adenoviral infection on the amplification of the cigarette smoke-induced lung inflammation which is present in severe emphysema. In addition to promoting an inflammatory process, lower respiratory viral or atypical bacterial infection may enhance the susceptibility of the airways to other pathogens [75, 76]. One example is chronic *Chlamydophila pneumoniae* infection in COPD patients, which has been associated with a higher rate of airway colonisation with common bacteria, frequent exacerbations and more severe functional impairment [75].

The identification of patients with this infective phenotype has therapeutic implications because long-term antibiotics can be effective in reducing the bacterial load and in modulating inflammation, resulting in a reduction in the frequency of exacerbations and improvement in the quality of life. This constitutes an example of a phenotype-guided treatment of COPD, as has been proposed recently (fig. 3) [77].

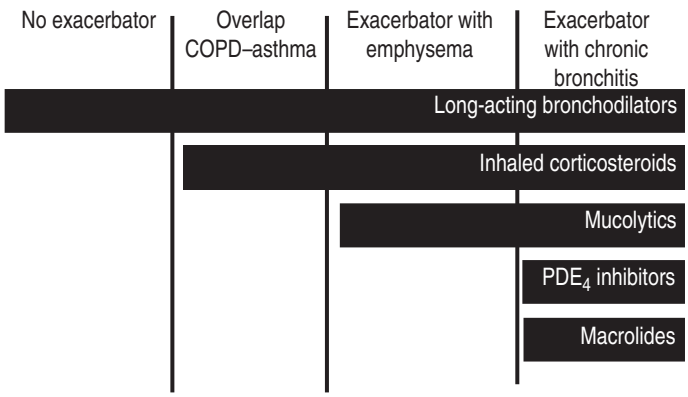

Figure 3. Proposal of pharmacological treatment of chronic obstructive pulmonary disease (COPD) according to clinical phenotypes. Bronchodilators are the basis of treatment of COPD irrespective of the clinical phenotype. Inhaled corticosteroids are indicated in frequent exacerbators and patients with the overlap COPD-asthma phenotype. Mucolytics can be used in frequent exacerbators, particularly if they have predominant chronic bronchitis and/or inhaled corticosteroids are not prescribed. Roflumilast is indicated in frequent exacerbators with chronic bronchitis. Finally, selected cases of patients with chronic bronchitis and frequent exacerbations, despite optimal therapy, may be candidates for treatment with long-term antibiotics under close follow-up in reference centres. The order of the bars does not represent the order of preference for treatment. PDE_4: phosphodiesterase-4. Reproduced from [77] with permission.

Conclusion

The impairment in host defences caused mainly by cigarette smoking facilitates the establishment and proliferation of PPMs in the bronchial tree of patients with chronic bronchial disease, particularly in the case of COPD. Repeated culture of PPMs in bronchial secretions in stable state was called bronchial colonisation; however, there is a growing body of evidence demonstrating the impact of bacteria and the related inflammation in the course of the disease. When the presence of a microorganism in a given tissue is associated with local and/or systemic consequences, the word ''colonisation'' is no longer adequate and the term chronic infection (or low-grade infection) is preferred. This is not just a change in denomination; the change from the concept of colonisation to a chronic infection implies the possibility of

treatment to prevent the consequences derived from infection. The concept of CBI justifies the development of clinical trials to investigate the impact of the long-term administration of antibiotics in the natural course of the disease, and particularly in the prevention of exacerbations.

Statement of Interest

N. Tudoric has received speakers and consultant's honoraria, as well as travel expenses to major scientific congresses from Boehringer Ingelheim, GSK, Merck, Novartis, Sandoz, Bayer and Pliva. M. Miravitlles has received speaker's fees from Boehringer Ingelheim, Pfizer, AstraZeneca, Bayer Schering, Novartis, Talecris-Grifols, Takeda-Nycomed, Merck, Sharp & Dohme and Novartis. He has also received consulting fees from Boehringer Ingelheim, Pfizer, GSK, AstraZeneca, Bayer Schering, Novartis, Almirall, Merck, Sharp & Dohme, Talecris-Grifols and Takeda-Nycomed.

References

1. Morris A, Sciurba FC, Lebedeva IP, *et al.* Association of chronic obstructive pulmonary disease severity and Pneumocystis colonization. *Am J Respir Crit Care Med* 2004; 170: 408–413.
2. Sethi S, Maloney J, Grove L, *et al.* Airway inflammation and bronchial bacterial colonisation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 991–998.
3. Marin A, Monso E, Garcia-Nunez M, *et al.* Variability and effects of bronchial colonisation in patients with moderate COPD. *Eur Respir J* 2010; 35: 295–302.
4. Patel IS, Seemungal TAR, Wilks M, *et al.* Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax* 2002; 57: 759–764.
5. Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
6. Rosell A, Monso E, Soler N, *et al.* Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med* 2005; 165: 891–897.
7. Monso E, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; 152: 1316–1320.
8. Wilkinson TMA, Patel IS, Wilks M, *et al.* Airway bacterial load and FEV_1 decline in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 167: 1090–1095.
9. Sethi S, Evans N, Grant BJB, *et al.* New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347: 465–471.
10. Miravitlles M. Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? *Eur Respir J* 2002; 20: Suppl. 36, 1s–11s.
11. Bresser P, Out TA, van Alphen L, *et al.* Airway inflammation in nonobstructive and obstructive chronic bronchitis with chronic *Haemophilus influenzae* airway infection. Comparison with noninfected patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 947–952.
12. Hill AT, Campbell EJ, Hill SL, *et al.* Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *Am J Med* 2000; 109: 288–295.
13. Garcha DS, Thurston SJ, Patel AR, *et al.* Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012; 67: 1075–1080.
14. Miravitlles M. Epidemiology of chronic obstructive pulmonary disease exacerbations. *Clin Pulm Med* 2002; 9: 191–197.
15. Veeramachaneni SB, Sethi S. Pathogenesis of bacterial exacerbations of COPD. *COPD* 2006; 3: 109–115.
16. Marin A, Garcia-Aymerich J, Sauleda J, *et al.* Effect of bronchial colonisation on airway and systemic inflammation in stable COPD. *COPD* 2012; 9: 121–130.
17. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 2355–2365.
18. Fuschillo S, Martucci M, Donner CF, *et al.* Airway bacterial colonization: the missing link between COPD and cardiovascular events? *Respir Med* 2012; 106: 915–923.
19. Sethi S. Infection as a comorbidity of COPD. *Eur Respir J* 2010; 35: 1209–1215.
20. Matkovic Z, Miravitlles M. Chronic bronchial infection in COPD. Is there an infective phenotype? *Respir Med* 2013; 107: 10–22.
21. Cabello H, Torres A, Celis R, *et al.* Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997; 10: 1137–1144.
22. Middleton AM, Dowling RB, Mitchell JL, *et al. Haemophilus parainfluenzae* infection of respiratory mucosa. *Respir Med* 2003; 97: 375–381.
23. Murphy TF, Brauer AL, Sethi S, *et al. Haemophilus haemolyticus*: a human respiratory tract commensal to be distinguished from *Haemophilus influenzae*. *J Infect Dis* 2007; 195: 81–89.
24. Soler N, Agusti C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 2007; 62: 29–35.

25. Weinreich UM, Korsgaard J. Bacterial colonisation of lower airways in health and chronic lung disease. *Clin Respir J* 2008; 2: 116–122.
26. Rogers DF. Physiology of airway mucus secretion and pathophysiology of hypersecretion. *Respir Care* 2007; 52: 1134–1146.
27. Berenson CS, Wrona CT, Grove LJ, *et al.* Impaired alveolar macrophage response to Haemophilus antigens in chronic obstructive lung disease. *Am J Respir Crit Care Med* 2006; 174: 31–40.
28. Taylor AE, Finney-Hayward TK, Quint JK, *et al.* Defective macrophage phagocytosis of bacteria in COPD. *Eur Respir J* 2010; 35: 1039–1047.
29. Soler N, Ewig S, Torres A, *et al.* Airway inflammation and bronchial microbial patterns in patients with stable chronic obstructive pulmonary disease. *Eur Respir J* 1999; 14: 1015–1022.
30. Monso E, Rosell A, Bonet G, *et al.* Risk factors for lower airway bacterial colonization in chronic bronchitis. *Eur Respir J* 1999; 13: 338–342.
31. Zalacain R, Sobradillo V, Amilibia J, *et al.* Predisposing factors to bacterial colonization in chronic obstructive pulmonary disease. *Eur Respir J* 1999; 13: 343–348.
32. Miravitlles M, Marin A, Monso E, *et al.* Colour of sputum is a marker for bacterial colonisation in chronic obstructive pulmonary disease. *Respir Res* 2010; 11: 58.
33. Banerjee D, Khair OA, Honeybourne D. Impact of sputum bacteria on airway inflammation and health status in clinical stable COPD. *Eur Respir J* 2004; 23: 685–691.
34. Murphy TF, Brauer AL, Schiffmacher AT, *et al.* Persistent colonization by *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 266–272.
35. Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; 50: 339–344.
36. Sethi S, Sethi R, Eschberger K, *et al.* Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 356–361.
37. Beasley V, Joshi PV, Singanayagam A, *et al.* Lung microbiology and exacerbations in COPD. *Int J Chron Obst Respir Dis* 2012; 7: 555–569.
38. Sze MA, Dimitriu PA, Hayashi S, *et al.* The lung tissue microbiome in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 185: 1073–1080.
39. Erb-Downward JR, Thompson DL, Han MK, *et al.* Analysis of the lung microbiome in the "healthy" smoker and in COPD. *PLoS One* 2011; 6: e16384.
40. Li M, Li Q, Yang G, *et al.* Cold temperature induces mucin hypersecretion from normal human bronchial epithelial cells *in vitro* through a transient receptor potential melastatin 8 (TRPM8)-mediated mechanism. *J Allergy Clin Immunol* 2011; 128: 626–634.
41. Foxwell AR, Kyd JM, Cripps AW. Nontypeable *Haemophilus influenzae*: pathogenesis and prevention. *Microbiol Mol Biol Rev* 1998; 62: 294–308.
42. Miravitlles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. *Respir Med* 2011; 105: 1118–1128.
43. van Alphen L, Jansen HM, Dankert J. Virulence factors in the colonization and persistence of bacteria in the airways. *Am J Respir Crit Care Med* 1995; 151: 2094–2099.
44. Martínez-Solano L, Macia MD, Fajardo A, *et al.* Chronic *Pseudomonas aeruginosa* infection in chronic obstructive pulmonary disease. *Clin Infect Dis* 2008; 47: 1526–1533.
45. Murphy TF. The role of bacteria in airway inflammation in exacerbations of chronic obstructive pulmonary disease. *Curr Opin Infect Dis* 2006; 19: 225–230.
46. Clemans DL, Bauer RJ, Hanson JA, *et al.* Induction of proinflammatory cytokines from human respiratory epithelial cells after stimulation by nontypeable *Haemophilus influenzae*. *Infect Immun* 2000; 68: 4430–4440.
47. Berenson CS, Murphy TF, Wrona CT, *et al.* Outer membrane protein P6 of nontypeable *Haemophilus influenzae* is a potent and selective inducer of human macrophage proinflammatory cytokines. *Infect Immun* 2005; 73: 2728–2735.
48. Hill A, Gompertz S, Stockley R. Factors influencing airway inflammation in chronic obstructive pulmonary disease. *Thorax* 2000; 55: 970–977.
49. Fuke S, Betsuyaku T, Nasuhara Y, *et al.* Chemokines in bronchiolar epithelium in the development of chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2004; 31: 405–412.
50. Sethi S, Muscarella K, Evans N, *et al.* Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 118: 1557–1565.
51. Bresser P, van Alphen L, Habets FJM, *et al.* Persisting *Haemophilus influenzae* strains induce lower levels of interleukin-6 and interleukin-8 in H292 lung epithelial cells than nonpersisting strains. *Eur Respir J* 1997; 10: 2319–2326.
52. Murphy TF, Brauer AL, Grant BJB, *et al. Moraxella catarrhalis* in chronic obstructive pulmonary disease: burden of disease and immune response. *Am J Respir Crit Care Med* 2005; 172: 195–199.
53. Murphy TF, Brauer AL, Eschberger K, *et al. Pseudomonas aeruginosa* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 853–860.
54. Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010; 137: 1091–1097.

55. Monsó E, Rosell A, Bonet G, *et al.* The impact of bronchial colonization on quality of life of patients with chronic, stable chronic bronchitis. *Med Clin (Barc)* 1998; 111: 561–564.
56. Kiechl S, Werner P, Egger G, *et al.* Active and passive smoking, chronic infections, and the risk of carotid atherosclerosis. Prospective results from the Bruneck study. *Stroke* 2002; 33: 2170–2176.
57. Tormakangas L, Erkkila L, Korhonen T, *et al.* Effects of repeated *Chlamydia pneumonia* inoculations on aortic lipid accumulation and inflammatory response in C57BL/6J mice. *Infect Immun* 2005; 73: 6458–6466.
58. Stockley RA, O'Brien C, Pye A, *et al.* Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. *Chest* 2000; 117: 1638–1645.
59. Miravitlles M, Kruesmann F, Haverstock D, *et al.* Sputum colour and bacteria in chronic bronchitis exacerbations: a pooled analysis. *Eur Respir J* 2012; 39: 1354–1360.
60. Llor C, Moragas A, Hernández S, *et al.* Efficacy of antibiotic therapy for acute exacerbations of mild to moderate COPD. *Am J Respir Crit Care Med* 2012; 186: 716–723.
61. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 117: 380S–385S.
62. Sapey E, Stockley RA. COPD exacerbations. 2: Aetiology. *Thorax* 2006; 61: 250–258.
63. Soler N, Torres A, Ewig S, *et al.* Bronchial microbial patterns in severe exacerbations of chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. *Am J Respir Crit Care Med* 1998; 157: 1498–1505.
64. Matkovic Z, Huerta A, Soler N, *et al.* Predictors of adverse outcome in patients hospitalised for exacerbation of chronic obstructive pulmonary disease. *Respiration* 2012; 84: 17–26.
65. Miravitlles M, Espinosa C, Fernandez-Laso E, *et al.* Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. *Chest* 1999; 116: 40–46.
66. Lode H, Allewelt M, Balk S, *et al.* A prediction model for bacterial etiology in acute exacerbations of COPD. *Infection* 2007; 35: 143–149.
67. Sethi S, Wrona C, Eschberger K, *et al.* Inflammatory profile of new bacterial strain exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 491–497.
68. Sethi S, Wrona C, Grant BJB, *et al.* Strain-specific immune response to *Haemophilus influenzae* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 448–453.
69. Bakri F, Brauer AL, Sethi S, *et al.* Systemic and mucosal antibody response to Moraxella catarrhalis after exacerbations of chronic obstructive pulmonary disease. *J Infect Dis* 2002; 185: 632–640.
70. Sethi S. New developments in the pathogenesis of acute exacerbations of chronic obstructive pulmonary disease. *Curr Opin Infect Dis* 2004; 17: 113–119.
71. Mallia P, Footitt J, Sotero R, *et al.* Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 1117–1124.
72. Martinez-Garcia MA, Soler-Cataluna JJ, Donat-Sanz Y, *et al.* Factors associated with bronchiectasis in chronic obstructive pulmonary disease patients. *Chest* 2011; 140: 1130–1137.
73. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
74. Retamales I, Elliott WM, Meshi B, *et al.* Amplification of inflammation in emphysema and its association with latent adenoviral infection. *Am J Respir Crit Care Med* 2001; 164: 469–473.
75. Blasi F, Damato S, Cosentini R, *et al. Chlamydia pneumoniae* and chronic bronchitis: association with severity and bacterial clearance following treatment. *Thorax* 2002; 57: 672–676.
76. Avadhanula V, Rodriguez CA, De Vincenzo JP, *et al.* Respiratory viruses augment the adhesion of bacterial pathogens to respiratory epithelium in a viral species- and cell type-dependent manner. *J Virol* 2006; 80: 1629–1636.
77. Miravitlles M, Soler-Cataluña JJ, Calle M, *et al.* Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur Respir J* 2013; 41: 1252–1256.

Chapter 6

Definition and aetiology of infective exacerbations of COPD

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SUMMARY: A standardised definition of infective exacerbation of chronic obstructive pulmonary disease (COPD) still represents an unmet need in respiratory medicine because it relies on clinical empiricism with little evidence-based scientific support. Infective exacerbations of COPD are certainly clear events in the mind of practising physicians. However, there is little consensus on their definition and relevance of different infective aetiologies. Indeed, the efforts to assess the efficacy of new therapies in the treatment and prevention of COPD exacerbations have been hampered by the lack of a widely agreed and consistently used definition. There is a strong need for greater investment in research on infective exacerbations of COPD in order to promote a better understanding and clinical approach of this event in the natural history of COPD.

Herein we will review the current concepts, definitions and aetiology of the infective exacerbations of COPD, underlining their strength and limitations.

KEYWORDS: Antibiotic, chronic obstructive pulmonary disease, cough, dyspnoea, sputum

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Eur Respir Monogr 2013; 60: 58–67.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017412
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and to noxious particles or gases in the lung [1]. COPD represents one of the most important causes of morbidity and mortality, and exposure to cigarette smoke and pollution represent the most important risk factors for the development of the disease. The human and social costs of this disease are enormous. It is estimated that in 2020, COPD will be the third cause of death in developed countries. The natural course of COPD is punctuated by recurrent events characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, and that may warrant a change in regular medication [1]. These events are defined exacerbations. Exacerbations, together with systemic comorbid conditions, contribute to the overall severity in individual COPD patients [1]. In addition to increasing COPD-associated morbidity and mortality [2], exacerbations contribute to loss of lung function [3, 4] and impaired health status in

COPD patients [5]. Therefore, prevention of exacerbations and/or reduction in exacerbation rate is a major outcome to be pursued in COPD management [1].

Bacterial and/or viral infections of the tracheobronchial tree are considered the most common causes of COPD exacerbations [6]. However, a standardised definition of an infective exacerbation of COPD is still an unmet need in respiratory medicine and no clinical and laboratory tools are available to drive the aetiological definition of a COPD exacerbation. Consequently, the indication for antimicrobial therapy is mainly empiric and, in particular for the outpatient setting, the relevance and utility of this pharmacological strategy is a much debated issue [7]. The Global Initiative for Obstructive Lung Disease (GOLD) guidelines recommend the administration of antibiotics to patients with bacterial exacerbations of COPD characterised by the presence of three cardinal symptoms (increased dyspnoea, increased sputum volume and increased sputum purulence) or with two cardinal symptoms, if increased sputum purulence is one of the two symptoms. Antibiotic treatment is also recommended in patients with a severe exacerbation of COPD that requires mechanical ventilation (invasive or noninvasive) [1].

Proposed definitions of COPD exacerbation: focus on infective exacerbations of COPD

Since Fletcher first described ''chest episodes'' [8], interest and research activity in the field of infective COPD exacerbations have increased steadily. Initially, most COPD exacerbation definitions were developed for studies of antibiotics for which bacterial exacerbations were required. From such research emerged the classic criteria of ANTHONISEN *et al.* [9], which has formed the basis of many subsequent definitions [10]. ANTHONISEN *et al.* [9] divided exacerbated COPD patients into three groups according to their symptoms: Type 1 have increased breathlessness, sputum volume and sputum purulence; Type 2 have two of these symptoms; and Type 3 have one of these symptoms, in addition to one of the following criteria: an upper respiratory tract infection in the past 5 days, fever without other cause, increased wheezing or cough, or an increase in heart rate or respiratory rate by 20% compared with baseline readings. There has been much debate over the last 20 years about how exactly a COPD exacerbation should be defined and two different approaches have been proposed.

Symptom-based definitions of COPD exacerbation

To this group belongs one of the most used definitions that identifies a COPD exacerbation as ''a sustained worsening of respiratory symptoms that requires a patient to seek medical help'' [11, 12]. A very similar, but looser, definition was proposed as a consensus definition of an experts' panel: ''a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD'' [13]. An exacerbation of COPD may also be defined as ''a sustained worsening of respiratory symptoms that is acute in onset and usually requires a patient to seek medical help or alter treatment'' [10]. The deterioration must be more severe than the usual daily variation experienced [14].

Another symptom based definition of COPD exacerbation used in large, controlled clinical trials of drugs includes the parameter of duration and indicates COPD exacerbations to be characterised by ''increase in dyspnoea, cough or associated with a change in quality and quantity of sputum that led the patient to seek medical attention and lasts for at least 3 days'' [15, 16]. However, there is no good evidence that 3 days of symptoms are required to define a COPD exacerbation.

Unlike the situation in asthma, patients with COPD do not experience sudden increases in symptoms that may disappear spontaneously or with medication within hours or a few days [17]. Moreover, delay in initiating treatment for an exacerbation may result in longer duration of the episode [18]. Consequently, no time limit should be required to define an exacerbation of COPD.

Another proposed definition of COPD exacerbation has been "an increase in respiratory symptoms over baseline that usually requires medical intervention" [19, 20].

There are a number of advantages and disadvantages to the use of a symptom-based definition [10]. Symptoms are of fundamental importance and are the primary concern of the patient; it is generally a change in symptoms that prompts contact with healthcare professionals [10]. Furthermore, approximately two-thirds of COPD patients are aware of when an exacerbation is imminent and in most cases symptoms are consistent from one exacerbation to another [21].

While some scales for symptom assessment do exist, the validity of the scales currently available and their sensitivity have not been established in COPD exacerbations [10]. The most common approach to capture symptom changes over time uses a paper-based diary card, but it is increasingly controversial as it is associated with a number of intrinsic disadvantages, the most problematic of which is an extremely poor adherence to protocol instructions and data validity issues arising from retrospective record entry [10].

COPD exacerbation rates reported on diary cards for symptom-based studies are higher than for event-based studies because a significant percentage (~50%) of exacerbations will not be reported to the physician or healthcare professional [22–25]. It has been suggested that this relates to the fact that patients with COPD may not understand their disease and the importance of seeking treatment, they may be depressed, or lack mobility. It can also sometimes reflect patient's self-treatment with "emergency" courses of antibiotics and/or glucocorticoids [26].

It also remains unclear whether these COPD exacerbations unreported to a physician are clinically relevant [22, 27]. However, patients who report a smaller proportion of their COPD exacerbations tend to have a poorer health-related quality of life [18]. This difference may be explained by the fact that these patients do not receive treatment and consequently their COPD exacerbations take longer to recover and have a greater impact on patients' perception of their disease [28].

Event-based definitions of COPD exacerbation

Event-based definitions of COPD exacerbations are increasingly used to capture all patients whose condition has changed enough to require an emergency visit, hospitalisation or a change of treatment (generally the addition of systemic glucocorticoids and/or antibiotics) [10]. Classification of COPD exacerbations based on events is widely used in clinical trials [10, 29–31].

Although this method captures fewer episodes than symptom-based definitions and selects a distinct patient subgroup with more severe COPD exacerbations, event-based definitions currently represent the most unambiguous and practical approach to clearly identifying episodes of COPD exacerbation [10]. It is important to note that these event-based definitions miss many symptom-related exacerbations that may be important for the patient. Indeed, it has been reported that only 63% of event-based COPD exacerbations were predicted by changes in individual symptoms [22]. Furthermore, changes in rescue medication use or peak expiratory flow were poor predictors of event-based exacerbations. The authors of the study concluded that: 1) event-based exacerbations are a valid way of identifying acute symptom change in COPD; and 2) that daily symptom monitoring is too variable to make individual management decisions using current methods [22]. In addition, event-based definitions of COPD exacerbation are limited by a reliance on factors other than the underlying disease. These include accessibility to healthcare and the social and financial situation of the patient [32].

Aetiology of infective exacerbations of COPD

Infections of the tracheobronchial tree, together with air pollution, are considered the most common causes of COPD exacerbations [6]. Many exacerbations are associated with symptoms of infection of the tracheobronchial tree, and bacteria have been classically considered the main infective cause of exacerbations [33]. However, determining the contribution of bacteria to

exacerbations is difficult as COPD patients are often colonised with bacteria even when clinically stable [6, 34, 35]. The proportion of patients with positive bacterial cultures and a high bacterial load increases during exacerbations in most, although not in all, studies [36, 37]. *Haemophilus influenzae, Moraxella catarrhalis* and *Streptococcus pneumoniae* are the most common bacteria found in the sputum of COPD patients during an exacerbation [1]. Newer molecular techniques have recently shown that colonisation is not a static condition and there is a frequent turnover of different strains of bacteria evoking specific host responses. Thus, it is likely that a change in the strain, but not the organism, may be responsible for the exacerbations [38]. Therefore, previous studies lacking in the molecular characterisation of bacterial strains may have missed evidence of a new infection. Indeed, it has been documented that the acquisition of a new strain of colonising bacteria increases the risk of an exacerbation.

In the past decades, the use of highly sensitive diagnostic methods, such as PCR, to evaluate the association between respiratory virus infections and COPD exacerbations has shown that viruses are responsible for a much higher proportion of exacerbations than was previously realised [6]. In a study of the East London COPD cohort, respiratory viruses were detected in 39% of exacerbations, the most common being rhinoviruses, which accounted for 58% of viruses [39]. A respiratory virus was detected in approximately 50% of patients with severe COPD exacerbation admitted to hospitals in Germany and Italy, with rhinovirus again being the most common [11, 40]. At variance with bacterial infections, the respiratory viruses more commonly found during exacerbations were virtually absent in stable state, suggesting that they play a relevant role in the aetiology of the acute episodes.

Until now, few studies have comprehensively investigated both bacteria and viruses during the same severe COPD exacerbations [11]. Infectious exacerbations had longer hospitalisations and greater impairment of several measures of lung function than non-infectious exacerbations. Importantly, exacerbations with co-infection had more marked lung function impairment and longer hospitalisations [11]. Interestingly, it has been recently shown that experimental rhinovirus infection in COPD patients leads to secondary bacterial airway infection suggesting that a substantial proportion of exacerbations attributed to bacterial infection alone may have been preceded and precipitated by viral infection, but the virus is no longer detectable at the time of presentation [41].

To date, no biomarker (alone or in combination with other biomarkers) has been found with good sensitivity and specificity that can reliably identify the aetiology of a COPD exacerbation [42], and/or is able to discriminate between bacterial or viral aetiology.

The colour of the purulent sputum during COPD exacerbations has been proposed in the past as a marker of bacterial infection and it is still considered a reason for starting the antibiotic treatment in the GOLD guidelines [1]. However, COPD exacerbations associated with purulent sputum production have been associated with a large bacterial load in some, but not all, studies [43–45]. Virtually all the studies that have found a relationship between bacterial infection and increased markers of neutrophilic inflammation in sputum samples and/or increased sputum purulence during exacerbation, did not take into account viral and/or viral/bacterial co-infections. Whether enhanced neutrophilic inflammation in the airways of COPD patients during exacerbation is a marker of bacterial infection has been debated in the past few years. Indeed, in experimental conditions, rhinovirus infection induces peripheral blood and sputum netrophilia in smokers and COPD subjects [46]. A recent study showed increased numbers of neutrophils in sputum during exacerbations and the neutrophilic response occurred irrespective of the pathogen detected (bacteria *versus* viruses *versus* co-infection viruses plus bacteria) [11]. The same study documented that purulent sputum at exacerbation was more frequent in infective exacerbations as compared to noninfective exacerbations but no difference was found between viral *versus* bacterial infections [11]. At variance with neutrophils, sputum eosinophils were significantly elevated at exacerbation only in the subgroups with viral infections suggesting that sputum eosinophilia and not sputum neutrophilia can be a marker of viral infection during COPD exacerbations [11].

In the past, two clinical trials have shown that many COPD exacerbations, of variable severity and different sputum purulence, may be managed without antibiotic therapy simply using the level of serum pro-calcitonin as a marker of the presence of bacterial infection [47, 48]. More recent studies have supported the use of pro-calcitonin for alerting clinicians to invasive bacterial infections such as pneumonia, but it does not reliably distinguish bacterial from viral and noninfectious causes of COPD exacerbations [49]. However, this remains an area of active ongoing research and novel biomarkers (such as serum hydrogen sulfide) are under investigation [50].

Classification of severity of infective exacerbations of COPD

No validated scale of severity exists for infective exacerbations of COPD [51]. Some authors have used a composite scale of symptoms to evaluate the resolution of the episode in clinical trials of antibiotics [52], or in observational follow-up studies [53]. However, to date, these scales have not been validated in long-term pharmacological clinical trials in stable COPD patients. In contrast, most studies have used the intensity of the medical intervention required during the acute phase as a grade of severity of COPD exacerbations, from self-management at home to admission to an intensive care unit (ICU) [51].

ANTHONISEN *et al.* [9] divided exacerbated COPD patients into three groups according to their symptoms and this definition has been widely used in clinical trials of antibiotics for exacerbations of COPD. However, it is not a severity scale, but a classification that indicates the likelihood of bacterial infection as cause of an exacerbation (*i.e.* a Type 1 exacerbation in a patient with mild COPD may have a better prognosis than a Type 3 exacerbation in a patient with severe COPD) [10].

Using this definition: 1) health-status score results are closely related to the exacerbation frequency, with worse health status in patients with frequent COPD exacerbations [18]; and 2) dyspnoea is the most common and important symptom of a COPD exacerbation [24]. The significance of the minor criteria of ANTHONISEN *et al.* [9] has never been formally studied [10].

Mild exacerbations of COPD may be defined as increased breathlessness, possibly associated with increased cough and sputum production, which force the patient to seek medical attention outside the hospital [17]. COPD exacerbations may be defined as severe when they are associated with acute respiratory failure or acute-on-chronic respiratory failure using standard criteria (arterial oxygen tension ($P_{a}O_{2}$) <8 kPa (60 mmHg) with or without arterial carbon dioxide tension ($P_{a}CO_{2}$) >6 kPa (45 mmHg) and hydrogen ion concentration >44 nM (pH<7.35)), based on arterial blood–gas measurement while breathing room air [16, 52]. Severe COPD exacerbations frequently require admission to hospital and/or ICU [17, 54].

There are no established criteria for assessing severity in less severely ill patients not requiring hospital assessment. In many studies, the necessity of a treatment with systemic glucocorticoids is considered a marker of more severe COPD exacerbation (severity B) with the others classified as mild/moderate (severity A) [55].

The most recent American Thoracic Society (ATS)/European Respiratory Society (ERS) COPD guidelines provide the following operational classification of severity of COPD exacerbations to help rank the clinical relevance of the episode and its outcome: level I: treated at home; level II: requires hospitalisation; and level III: leads to respiratory failure [56]. The major limitation of this classification is that many COPD exacerbations requiring hospitalisation (level II) are associated with respiratory failure (level III). The criteria for hospital admission may also vary from country to country and in different hospitals.

The proposed severity classification of the recent ATS/ERS statement on outcomes for COPD pharmacological trials includes three categories: mild: increase in respiratory symptoms controlled by the patient with an increase in the usual medication; moderate: requiring treatment with systemic glucocorticoids and/or antibiotics; and severe: requiring hospitalisation or a visit to the emergency department [51]. The methodology surrounding the use of severity of a COPD exacerbation as a variable has not been standardised [51].

Many large, controlled clinical trials have defined a severe COPD exacerbation when it requires the introduction of a cycle of treatment with oral glucocorticoids and/or antibiotics [20, 30]. The clinical relevance of this approach is, at best, controversial due to the questionable magnitude of the effect of antibiotics and the small effect of systemic glucocorticoids on COPD exacerbations [57, 58]. Most cases of severe COPD exacerbations occur in patients with GOLD stage III or IV [59, 60]. In the long-term, patients who experience severe COPD exacerbations have an increased risk of experiencing more severe exacerbations in the future [53, 61].

Differential diagnosis of COPD exacerbations, including infective exacerbations of COPD

A prerequisite for a COPD exacerbation is that the patient has known COPD [62]. It may be difficult to distinguish a COPD exacerbation, including infective exacerbations of COPD, from other diseases presenting with similar clinical features during the first documented episode. This is very important, because, for example, a severe asthmatic exacerbation in an old smoking asthmatic patient may be easily confused with an exacerbation of COPD if the presence of asthma is unknown to the physician in charge of the patient [63]. Similarly, bronchiectasis is often confused in general practice with COPD [64, 65].

Furthermore, patients with a definite COPD diagnosis may also often have co-morbidities that need to be considered in the differential diagnosis when looking for other possible causes of acute deterioration of respiratory symptoms, outside of a true COPD exacerbation, including infective exacerbations of COPD [66, 67]. The commonest of these are represented by acute heart failure [64], pneumonia [68], pulmonary thromboembolism (PTE) [69–72], cardiac arrhythmia (mainly atrial fibrillation) [73], pneumothorax [74, 75] and lung cancer, among others [76]. These clinical conditions, even when co-existing (*e.g.* heart failure), should always be considered in the differential diagnosis of a true COPD exacerbation.

The measurement of the serum level of brain natriuretic peptide (BNP), or its precursor N-terminal (NT)-proBNP, and troponins may be useful in the differential diagnosis of the cause (cardiogenic *versus* pulmonary) of acute dyspnoea in a COPD patient [77–79]; although the broad overlap in BNP and NT-proBNP concentrations suggests poor specificity in this target patient population [80]. For this reason, clinical judgment must always be part of the evaluation of BNP or NT-proBNP assay results [81]. Novel biomarkers of heart failure are under active investigation [82]. More recently, when available, it has also been claimed the utility of bedside lung ultrasound in the differential diagnosis between pulmonary oedema and COPD exacerbations [83–87].

Interestingly, the presence of COPD does not affect the diagnostic performance of clinical probability estimate, D-dimer testing, spiral computed tomographic angiography or pulmonary angiography in the diagnosis of PTE in these patients [88].

The need for a standardised definition of infective exacerbation of COPD in controlled clinical trials

Many symptom- and event-based definitions of COPD exacerbation have been adopted in controlled clinical trials of drugs used for the treatment and prevention of COPD exacerbation [10]. Controlled clinical trials of old and new drugs conducted today still use a wide variety of definitions by which treatment success is judged, with increasing focus on event-based definitions of COPD exacerbations [20, 30, 57, 58, 89, 90]. There is, however, no evidence of improving consistency and many publications still feature inadequate descriptions of the definition and aetiology of infective COPD exacerbations. The lack of a consistent definition and aetiology of COPD exacerbation makes comparison of study findings and treatment effect virtually impossible [10].

The choice of definition of infective COPD exacerbations can significantly affect study outcomes, with varying criteria likely to result in different levels of demonstrated treatment success [10].

Conclusions

The definition and aetiology of infective exacerbations of COPD still relies on clinical empiricism with very little scientific support. As often happens when reviewing the literature on a clinical topic, one finds more questions than answers. Exacerbations of COPD are certainly clear events in the mind of practising physicians. However, when one tries to provide simple concepts such as definition and aetiology, you realise how little we know [10, 14, 32]. Efforts to assess the efficacy of new therapies in the treatment and prevention of COPD exacerbations have been hampered by the lack of a widely agreed and consistently used definition. This conclusion should reinforce the necessity of greater investment in research on the definition and aetiology of COPD exacerbations in order to promote a better understanding and clinical approach of this sometimes dramatic event in the natural history of COPD. New potential directions of research for this topic may be represented by the ongoing active development of virus and bacteria experimental human models of COPD exacerbations [41, 46, 91–95].

Statement of Interest

A. Papi has received fees for consultancy, lectures and advisory boards, and has received travel expenses reimbursements or research grants from: AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Menarini, Mundipharma International, Novartis, Nycomed and Zambonno.

References

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. www.goldcopd.org Date last accessed: January 2013.
2. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.
3. Donaldson GC, Seemungal TA, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
4. Contoli M, Baraldo S, Marku B, *et al.* Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol* 2010; 125: 830–837.
5. Seemungal TA, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
6. Mallia P, Contoli M, Caramori G, *et al.* Exacerbations of asthma and chronic obstructive pulmonary disease (COPD): focus on virus induced exacerbations. *Curr Pharm Des* 2007; 13: 73–97.
7. Vollenweider DJ, Jarrett H, Steurer-Stey CA, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 12: CD010257.
8. Fletcher CM. Letter: Natural history of chronic bronchitis. *Br Med J* 1976; 1: 1592–1593.
9. Anthonisen NR, Manfreda J, Warren CP, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
10. Pauwels R, Calverley P, Buist AS, *et al.* COPD exacerbations: the importance of a standard definition. *Respir Med* 2004; 98: 99–107.
11. Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
12. Thompson AB, Daughton D, Robbins RA, *et al.* Intraluminal airway inflammation in chronic bronchitis. Characterization and correlation with clinical parameters. *Am Rev Respir Dis* 1989; 140: 1527–1537.
13. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest* 2000; 117: 398S–401S.
14. Currie GP, Wedzicha JA. ABC of chronic obstructive pulmonary disease. Acute exacerbations. *BMJ* 2006; 333: 87–89.
15. Casaburi R, Mahler DA, Jones PW, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.
16. Decramer M, Rutten-van Molken M, Dekhuijzen PN, *et al.* Effects of *N*-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; 365: 1552–1560.
17. Fabbri L, Beghe B, Caramori G, *et al.* Similarities and discrepancies between exacerbations of asthma and chronic obstructive pulmonary disease. *Thorax* 1998; 53: 803–808.
18. Wilkinson TM, Donaldson GC, Hurst JR, *et al.* Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 1298–1303.

19. Burge PS, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
20. Calverley P, Pauwels R, Vestbo J, *et al.* Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449–456.
21. Kessler R, Stahl E, Vogelmeier C, *et al.* Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest* 2006; 130: 133–142.
22. Calverley P, Pauwels Dagger R, Lofdahl CG, *et al.* Relationship between respiratory symptoms and medical treatment in exacerbations of COPD. *Eur Respir J* 2005; 26: 406–413.
23. Miravitlles M, Ferrer M, Pont A, *et al.* Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax* 2004; 59: 387–395.
24. Seemungal TA, Donaldson GC, Bhowmik A, *et al.* Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1608–1613.
25. Vijayasaratha K, Stockley RA. Reported and unreported exacerbations of COPD: analysis by diary cards. *Chest* 2008; 133: 34–41.
26. O'Reilly JF, Williams AE, Holt K, *et al.* Defining COPD exacerbations: impact on estimation of incidence and burden in primary care. *Prim Care Respir J* 2006; 15: 346–353.
27. Aaron SD, Fergusson D, Marks GB, *et al.* Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. *Thorax* 2008; 63: 122–128.
28. Donaldson GC, Wedzicha JA. COPD exacerbations. 1: Epidemiology. *Thorax* 2006; 61: 164–168.
29. Aaron SD, Vandemheen KL, Fergusson D, *et al.* Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007; 146: 545–555.
30. Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
31. Calverley PM, Boonsawat W, Cseke Z, *et al.* Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J* 2003; 22: 912–919.
32. Hurst JR, Wedzicha JA. What is (and what is not) a COPD exacerbation: thoughts from the new GOLD guidelines. *Thorax* 2007; 62: 198–199.
33. Wedzicha JA, Seemungal T. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786–796.
34. Gump DW, Phillips CA, Forsyth BR, *et al.* Role of infection in chronic bronchitis. *Am Rev Respir Dis* 1976; 113: 465–474.
35. Sethi S, Maloney J, Grove L, *et al.* Airway inflammation and bronchial bacterial colonization in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 991–998.
36. Monso E, Ruiz J, Rosell A, *et al.* Bacterial infection in chronic obstructive pulmonary disease. A study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med* 1995; 152: 1316–1320.
37. Rosell A, Monsó E, Soler N, *et al.* Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med* 2005; 165: 891–897.
38. Sethi S, Evans N, Grant BJ, *et al.* New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 2002; 347: 465–471.
39. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
40. Rohde G, Wiethege A, Borg I, *et al.* Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; 58: 37–42.
41. Mallia P, Footitt J, Sotero R, *et al.* Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 1117–1124.
42. Blasi F, Bocchino M, Di Marco F, *et al.* The role of biomarkers in low respiratory tract infections. *Eur J Intern Med* 2012; 23: 429–435.
43. Soler N, Augusti C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease (COPD). *Thorax* 2007; 62: 29–35.
44. Sethi S, Muscarella K, Evans N, *et al.* Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 118: 1557–1565.
45. Aaron SD, Angel JB, Lunau M, *et al.* Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 349–355.
46. Mallia P, Message SD, Gielen V, *et al.* Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med* 2011; 183: 734–742.
47. Stolz D, Christ-Crain M, Bingisser R, *et al.* Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007; 131: 9–19.
48. Christ-Crain M, Jaccard-Stolz D, Bingisser R, *et al.* Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004; 363: 600–607.

49. Falsey AR, Becker KL, Swinburne A, *et al.* Utility of serum procalcitonin values in patients with acute exacerbations of chronic obstructive pulmonary disease: a cautionary note. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 127–135.
50. Chen YH, Yao WZ, Gao JZ, *et al.* Serum hydrogen sulfide as a novel marker predicting bacterial involvement in patients with community-acquired lower respiratory tract infections. *Respirology* 2009; 14: 746–752.
51. Cazzola M, MacNee W, Martinez FJ, *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416–469.
52. Allegra L, Grassi C, Grossi E. Ruolo degli antibiotici nel trattamento delle riacutizzazioni della bronchite cronica: risultati di uno studio italiano multicentrico [Role of antibiotics in the treatment of chronic bronchitis exacerbations: results from an Italian multicentric study]. *Ital J Chest Dis* 1991; 45: 138–148.
53. Donaldson GC, Seemungal TA, Patel IS, *et al.* Longitudinal changes in the nature, severity and frequency of COPD exacerbations. *Eur Respir J* 2003; 22: 931–936.
54. Connors AF Jr, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; 154: 959–967.
55. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J* 2003; 21: Suppl. 41, 46s–53s.
56. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
57. Niewoehner DE. The role of systemic corticosteroids in acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Med* 2002; 1: 243–248.
58. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 19: CD004403.
59. Cao Z, Ong KC, Eng P, *et al.* Frequent hospital readmissions for acute exacerbation of COPD and their associated factors. *Respirology* 2006; 11: 188–195.
60. Tsoumakidou M, Tzanakis N, Voulgaraki O, *et al.* Is there any correlation between the ATS, BTS, ERS and GOLD COPD's severity scales and the frequency of hospital admissions? *Respir Med* 2004; 98: 178–183.
61. Garcia-Aymerich J, Monso E, Marrades RM, *et al.* Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. EFRAM study. *Am J Respir Crit Care Med* 2001; 164: 1002–1007.
62. Soto FJ, Varkey B. Evidence-based approach to acute exacerbations of COPD. *Curr Opin Pulm Med* 2003; 9: 117–124.
63. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. www.ginasthma.org Date last accessed: January 2013.
64. O'Brien C, Guest PJ, Hill SL, *et al.* Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635–642.
65. Patel IS, Vlahos I, Wilkinson TM, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400–407.
66. Martinez CH, Han MK. Contribution of the environment and comorbidities to chronic obstructive pulmonary disease phenotypes. *Med Clin North Am* 2012; 96: 713–727.
67. Patel AR, Hurst JR. Extrapulmonary comorbidities in chronic obstructive pulmonary disease: state of the art. *Expert Rev Respir Med* 2011; 5: 647–662.
68. Lieberman D, Gelfer Y, Varshavsky R, *et al.* Pneumonic *vs* nonpneumonic acute exacerbations of COPD. *Chest* 2002; 122: 1264–1270.
69. Ambrosetti M, Ageno W, Spanevello A, *et al.* Prevalence and prevention of venous thromboembolism in patients with acute exacerbations of COPD. *Thromb Res* 2003; 112: 203–207.
70. Erelel M, Cuhadaroglu C, Ece T, *et al.* The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. *Respir Med* 2002; 96: 515–518.
71. Rutschmann OT, Cornuz J, Poletti PA, *et al.* Should pulmonary embolism be suspected in exacerbation of chronic obstructive pulmonary disease? *Thorax* 2007; 62: 121–125.
72. Tillie-Leblond I, Marquette CH, Perez T, *et al.* Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: prevalence and risk factors. *Ann Intern Med* 2006; 144: 390–396.
73. Ramanuja S, Mastronarde J, Dowdeswell I, *et al.* A 44-year-old man with suspected exacerbation of COPD and atrial fibrillation. *Chest* 2004; 125: 2340–2344.
74. Emerman CL, Cydulka RK. Evaluation of high-yield criteria for chest radiography in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* 1993; 22: 680–684.
75. Sherman S, Skoney JA, Ravikrishnan KP. Routine chest radiographs in exacerbations of chronic obstructive pulmonary disease. Diagnostic value. *Arch Intern Med* 1989; 149: 2493–2496.
76. Caramori G, Papi A. Pathogenic link between chronic obstructive pulmonary disease and squamous cell lung cancer. *Expert Rev Respir Med* 2007; 1: 171–175.
77. Abroug F, Ouanes-Besbes L, Nciri N, *et al.* Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. *Am J Respir Crit Care Med* 2006; 174: 990–996.
78. Lehman R, Doust J, Glasziou P. Cardiac impairment or heart failure? *BMJ* 2005; 331: 415–416.
79. Mueller C, Scholer A, Laule-Kilian K, *et al.* Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004; 350: 647–654.

80. Murray H, Cload B, Collier CP, *et al.* Potential impact of N-terminal pro-BNP testing on the emergency department evaluation of acute dyspnea. *CJEM* 2006; 8: 251–258.
81. Januzzi JL Jr. Natriuretic peptide testing: a window into the diagnosis and prognosis of heart failure. *Cleve Clin J Med 2006; 73*, 149–152: 155–157.
82. Ahmad T, Fiuzat M, Felker GM, *et al.* Novel biomarkers in chronic heart failure. *Nat Rev Cardiol* 2012; 9: 347–359.
83. Cardinale L, Volpicelli G, Binello F, *et al.* Clinical application of lung ultrasound in patients with acute dyspnea: differential diagnosis between cardiogenic and pulmonary causes. *Radiol Med* 2009; 114: 1053–1064.
84. Gargani L, Fontana M, Sicari R, *et al.* Differential diagnosis of dyspnea: the incremental value of lung ultrasound. *Rec Prog Med* 2010; 101: 78–82.
85. Neesse A, Jerrentrup A, Hoffmann S, *et al.* Prehospital chest emergency sonography trial in Germany: a prospective study. *Eur J Emerg Med* 2012; 19: 161–166.
86. Volpicelli G, Cardinale L, Garofalo G, *et al.* Usefulness of lung ultrasound in the bedside distinction between pulmonary edema and exacerbation of COPD. *Emerg Radiol* 2008; 15: 145–151.
87. Zechner PM, Aichinger G, Rigaud M, *et al.* Prehospital lung ultrasound in the distinction between pulmonary edema and exacerbation of chronic obstructive pulmonary disease. *Am J Emerg Med* 2010; 28: 389.
88. Hartmann IJ, Hagen PJ, Melissant CF, *et al.* Diagnosing acute pulmonary embolism: effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiography. ANTELOPE Study Group. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism. *Am J Respir Crit Care Med* 2000; 162: 2232–2237.
89. Decramer M, Celli B, Tashkin DP, *et al.* Clinical trial design considerations in assessing long-term functional impacts of tiotropium in COPD: the UPLIFT trial. *COPD* 2004; 1: 303–312.
90. Wedzicha JA, Calverley PM, Seemungal TA, *et al.* The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177: 19–26.
91. Contoli M, Caramori G, Mallia P, *et al.* A human rhinovirus model of chronic obstructive pulmonary disease exacerbations. *Contrib Microbiol* 2007; 14: 101–112.
92. Hoogerwerf JJ, de Vos AF, Bresser P, *et al.* Lung inflammation induced by lipoteichoic acid or lipopolysaccharide in humans. *Am J Respir Crit Care Med* 2008; 178: 34–41.
93. Kharitonov SA, Sjobring U. Lipopolysaccharide challenge of humans as a model for chronic obstructive lung disease exacerbations. *Contrib Microbiol* 2007; 14: 83–100.
94. Reynier F, De Vos AF, Hoogerwerf JJ, *et al.* Gene expression profiles in alveolar macrophages induced by lipopolysaccharide in humans. *Mol Med* 2012; 18: 1303–1311.
95. Van der Merwe R, Molfino NA. Challenge models to assess new therapies in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 597–605.

Chapter 7

The role of viruses in chronic bronchitis and exacerbations of COPD

Gernot G.U. Rohde

SUMMARY: Respiratory viral infections belong to the most frequent infectious diseases. Small children in particular, but also elderly patients with underlying comorbidity such as chronic airways disease, are affected. The clinical course is often self-limiting but can be severe during exacerbations. There is a great diversity of respiratory viruses. This chapter introduces the most important respiratory viruses and comments on their specific role in chronic bronchitis and exacerbations of chronic obstructive pulmonary disease (COPD). Human rhinoviruses are most frequently detected in exacerbations of COPD. The inflammatory response of the airways to rhinoviruses leads to increased symptoms and exacerbations. Other important respiratory viruses include influenza, respiratory syncytial virus (RSV) and coronaviruses. In stable COPD, RSV seems to play a particular role, probably due to latent infection and effects on the underlying airways inflammation.

KEYWORDS: Human, infection, influenza, respiratory, respiratory syncytial virus, rhinovirus

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Eur Respir Monogr 2013; 60: 68–75.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017512
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Respiratory viral infections are frequent and common events. The mean yearly incidence is approximately six illnesses per year in children below the age of 1 year, which steadily declines as the immune system matures [1]. A slight increase in incidence has been observed in young adults between the age of 20 and 30 years, most probably due to increased exposure to small children [1]. The common cold, an illness triggered most frequently by respiratory infection with human rhinoviruses, is the most prevalent clinical presentation [2]. Other respiratory viruses associated with the common cold, as well as lower respiratory tract infections (LRTI), are influenza viruses, coronaviruses, parainfluenza viruses, respiratory syncytial virus (RSV) and enteroviruses [3]. However, the detection frequencies vary depending on numerous factors, such as season, viral sampling and detection methods, as well as age. Data from the USA suggest that about 25 million people visit their family doctors with uncomplicated upper respiratory infections and that the common cold syndrome results in about 20 million days of absence from work and 22 million days of absence from school [4]. Importantly, in patients with chronic airways diseases such as asthma, chronic bronchitis or chronic obstructive pulmonary disease (COPD), these respiratory viral infections can lead to much more severe clinical presentations such as exacerbations of disease.

Respiratory viral infections show a virus-specific seasonal pattern. Rhinoviruses are isolated throughout the year. However, the peak occurs at the beginning of the school year usually in September, presumably because contact among children increases [5]. The seasonal peak of influenza virus occurs during the winter months (December through to early April, depending on the virus type) [6]. RSV shows a seasonal pattern comparable to influenza. This can render the clinical distinction between these two different viruses difficult [7]. Coronaviruses are the third family of respiratory viruses with a clear detection peak in winter [2]. Parainfluenza viruses can be detected throughout the year with clear peaks in early fall and during the winter [8]. Adenoviruses, probably the most frequent only DNA viruses, are detected throughout the year without a clear seasonal predominance [2].

There are three main routes by which respiratory viruses can be transmitted: 1) direct hand contact with secretions that contain the virus, either directly from an infected person or indirectly from environmental surfaces; 2) inhalation of small-particle aerosols lingering in the air for an extended time; or 3) direct hit by large-particle aerosols from an infected person [4]. These routes of transmission do differ between viruses. Influenza viruses are believed to be mainly spread *via* small-particle aerosols [9], whereas rhinioviruses are probably transmitted mainly by direct hand contact followed by self-inoculation with the virus into the nose or eye [10]. Nevertheless, aerosol transmission of rhinoviruses has also been clearly documented [11].

The respiratory viruses

Rhinoviruses

Rhinovirus infection begins in the anterior nasal mucosa or in the eye. Mucociliary action moves the viruses to the posterior nasopharynx where the viruses gain entrance to epithelial cells in the adenoid area by binding to specific receptors on the cells. The viruses are quickly internalised and replication starts immediately. As an example, progeny viruses can be detected within 8–10 h after experimental intranasal inoculation of rhinoviruses [12]. Only a very small infectious dose of rhinovirus is needed [13], and most individuals without pre-existing virus-specific antibodies will be infected. For reasons still unknown, only three out of four infected persons develop symptomatic colds. Rhinoviruses do not cause damage to the respiratory epithelium, thus the development of symptoms is most probably related to indirect inflammatory processes.

Coronaviruses

Coronaviruses usually cause upper respiratory tract infections epidemically every 2–3 years. Coronavirus serotypes 229E and OC43 are the best known types. Recently, a new, highly pathogenic coronavirus (severe acute respiratory syndrome; SARS) was discovered [14], as well as other less pathogenic types (NL63) [15]. In September 2012, another novel coronavirus was detected whose properties are still largely unknown [16].

Adenoviruses

Adenoviruses are quite resistant to chemical or physical agents and can survive longer outside the body. They usually cause mild infections of the upper or lower respiratory tract, but also gastrointestinal infections and conjunctivitis. In immunosuppressed patients, adenovirus pneumonia is a feared complication with mortality rates of up to 50%.

Respiratory syncytial virus

Respiratory syncytial virus, commonly referred to as RSV, belongs to the *Paramyxoviridae* family, which includes common respiratory viruses such as those causing measles and mumps [17]. It is sensitive to physical or chemical agents. Frequent mutations in the immunogenic proteins render

recurrent infections possible. It is highly contagious and the most important pathogen in respiratory bronchiolitis in children; spread is mainly by direct contact. North-American studies suggest that RSV may also be an important pathogen in the elderly [17].

Human metapneumovirus

Human metapneumovirus was first discovered in 2001 using new molecular techniques for identification of unknown viruses growing in cultured cells of children with acute respiratory infections [18]. It is also grouped into the *Paramyxoviridae* family. It has been identified as a pathogen of upper respiratory tract infections, bronchiolitis, pneumonia, asthma and COPD exacerbations [19]. It shows a worldwide distribution with seasonal peaks similar to RSV. Seroprevalence is >90% at the age of 5 years.

Influenza

Influenza viruses have a segmented genome, which allows the exchange of gene segments during simultaneous infection of a cell facilitating the generation of new virus types. This is called ''antigenic shift''. ''Antigenic drift'' describes the frequent genomic mutations resulting in changes in the main immunogenic surface proteins haemagglutinin and neuraminidase [20]. Influenza viruses mainly infect the tracheobronchial epithelium and lead to extensive epithelial damage. Influenza infections are responsible for epidemics yearly with considerable morbidity and mortality. If antigenic shift takes place, influenza viruses can occur against which no protective serum antibodies exist in the population. This can lead to pandemics, such as with the occurrence of nH1N1 in 2009 [21].

Details of respiratory viruses

A detailed list of respiratory viruses and their virological properties is presented in table 1.

Respiratory viruses in exacerbations of chronic airways diseases

Historically, respiratory bacterial infections were believed to trigger up to 50% of exacerbations of chronic bronchitis and/or COPD whereas viral infections were detected in only 10–30% [27]. The fact that COPD exacerbations follow a seasonal pattern with more frequent events during the cold months raised the suspicion that viral infections may play a more important role than previously thought [28]. Epidemiological studies showed a correlation between the increase of influenza activity and hospital admissions for exacerbations of COPD [29], suggesting that respiratory viral infection might trigger COPD exacerbations. These figures come from prospective studies performed in the late 1970s and early 1980s [30–32]. A major limitation of these early studies was that they only were able to use virus culture and serology for the detection of respiratory viruses, techniques with limited sensitivity, particularly for the detection of human rhinoviruses, the most frequent species of respiratory viruses. The development of new diagnostic techniques, particularly PCR, allowed more sensitive detection of respiratory viruses [33, 34], and led to a revision of the role of respiratory viruses in chronic airways disease. The utility and importance of PCR for the detection of respiratory viruses was first demonstrated during the 1990s in children [34] and later, particularly in children with asthma [35]. At the beginning of the 21st century the first reports on the prevalence of respiratory viruses in COPD using PCR techniques were published. Results from the East London COPD study revealed that approximately 40% of exacerbations in COPD outpatients were associated with PCR detection of respiratory viruses [36]. It was shown 2 years later that respiratory viruses were also frequently detected by PCR in patients with more severe exacerbations necessitating hospital admission. Of these, 56% of patients were PCR positive [37]. Subsequent studies confirmed that detection of respiratory viral infection by PCR is more frequent than previously thought and found respiratory viruses in 46% [38], 42% [39], 48% [40], 43% [41] and 37% of exacerbations [42].

Table 1. Respiratory viruses

Virus	Size nm	Genome	Serotypes	Receptor
Rhinoviruses	30	Positive-sense, single-stranded RNA	>100	Major group: ICAM-1 [22] Minor group: vLDL [23]
Coronaviruses	60–220	Positive-sense, single-stranded RNA	Many	ACE2 [24]
Adenoviruses	90–100	Double-stranded linear DNA	>47	Group B: CD46 [25] All other: CAR [26]
RSV	120–300	Negative-sense, single-stranded RNA	A and B	Unknown
hMPV	~200	Negative-sense, single-stranded RNA	A and B	Unkown
Influenza	80–120	Single-stranded RNA	Many	Sialic acid

RSV: respiratory syncytial virus; hMPV: human metapneumovirus; ICAM-1: intercellular adhesion molecule-1; vLDL: very low-density lipoprotein; ACE2: angiotensin converting enzyme-2; CAR: coxsackie-adenovirus receptor.

Human rhinoviruses are by far the most frequently detected respiratory viruses during acute exacerbations of COPD (AECOPD). In different studies they represent 13.8–50.7% of all viruses detected. This corresponds to a detection rate of 3.3–24.7% (table 2) [36, 37, 40, 42–44]. The second most frequent group of respiratory viruses are influenza representing 7.8–32.8% of all respiratory viruses detected, corresponding to a detection rate of 3.6–17.8% (table 2) [37–39, 44–47]. RSV is a unique virus as it is frequently detected during exacerbations of COPD [37, 45, 47, 48], but also during the stable phase (table 2) [36, 49–52].

The other respiratory RNA viruses such as coronaviruses, influenza B and parainfluenza viruses are less frequently detected. In recent years some new respiratory viruses have emerged, particularly in the paediatric population. Human metapneumovirus was first identified by viral culture in 2001 in respiratory secretions of children with LRTI [18]. Studies in COPD patients with acute exacerbations revealed that it was seldom detectable [19, 39, 53]. In 2003, SARS, a novel and highly pathogenic coronavirus, emerged [14], but subsequent research showed no particular role in COPD patients [54]. Isolation from a DNase-treated pooled respiratory specimen using random amplification, cloning und large-scale sequencing led to the identification of human bocavirus in 2005 [55]. This virus was mainly found in children [56]. It does not seem to play an important role in adults [57]. In 2007, new human papillomaviruses were first identified, again in respiratory secretion of a child [58]. As with some of the viruses discussed previously, no evidence of infection in COPD patients was found for this virus [59]. Again this might be related to an age-related pattern of infection [60].

Table 2. Frequency of respiratory viral detection in acute exacerbations of chronic obstructive pulmonary disease

Virus	Viruses detected %	Detection rate %
Rhinovirus	13.8–50.7	3.3–24.7
Influenza A	7.8–32.8	3.6–17.7
RSV	10.3–24.7	2.4–15.3
Coronavirus	9.1–20.7	4.1–4.9
Influenza B	3.9–12.1	1.8–4.7
PIV 1–4	1.3–10.0	0.6–7.1
Adenovirus	1.3–1.7	0.4–7.0
EBV		58[#]
hMPV	1.7	0.4–2.3

RSV: respiratory syncytial virus; PIV: parainfluenza virus; EBV: Epstein–Barr virus; hMPV: human metapneumovirus. [#]: this refers to only one study exclusively investigating EBV, this finding has not been repeated in other studies.

The mere detection of pathogens does not necessarily represent virulence and it is difficult to prove that pathogens

detected are actually the triggers of an exacerbation. This is true for bacteria as well as for viruses. There are some important arguments that support a triggering role of viruses in AECOPD. It has been shown that recovery from viral exacerbations is significantly longer than from non-viral exacerbations [36]. Moreover, it has been shown that viral exacerbations are associated with more pronounced increases in airways inflammation that non-viral ones [61]. Experimental rhinovirus infection of COPD patients resulted in lower respiratory symptoms, airflow obstruction, and systemic and airways inflammation that were greater and more prolonged compared with the non-infected group. Neutrophil markers in sputum related to clinical outcomes and virus load correlated with inflammatory markers, which strongly suggests triggering of exacerbations by rhinoviruses [62]. More research is needed to further investigate the precise mechanisms of viral infections and their role in AECOPD.

Respiratory viruses in stable disease

In many of the studies using PCR techniques for the detection of the respiratory viruses mentioned previously, respiratory viruses were also detected during the stable phase of the disease. In the study by SEEMUNGAL *et al.* [36], respiratory viruses were found in 14.7% (10 out of 68) of samples from patients with stable COPD (five rhinoviruses, four coronaviruses and one parainfluenza virus). Approximately 50% had the same virus at stable and exacerbation sampling (three parainfluenza, three coronavirus and three rhinoviruses). RSV was detected in 23.5% (16 out of 68) of stable patients, nearly at the same detection frequency as during an exacerbation. Moreover, they found that patients who were RSV positive had, at least once, greater stable plasma fibrinogen, interleukin (IL)-6 and higher stable median arterial carbon dioxide. This was interpreted as low-grade infection. In addition, in the hospital-based study of ROHDE *et al.* [37], respiratory viruses were detected in 19% (eight out of 42) of the stable patients. In a subsequent study these authors evaluated a new PCR technique (real-time PCR) which allowed them to quantify the amount of respiratory viruses and to compute a viral load [63]. It was shown that RSV could indeed be detected at similar frequencies (28%) in stable and exacerbated COPD patients, and that the viral load was similarly low in both groups. In children with proven acute respiratory infection the viral load was 2000 times higher. In a mouse model of experimental RSV infections it was shown that RSV can persist for up to 60 days after infection [64]. In a cotton rat model in naïve animals and animals rendered immune to RSV by prior RSV infection, it was demonstrated that even though no virus could be isolated from the lungs of RSV-challenged immune animals, RSV infection in fact took place and an accumulation of viral RNA transcripts was observed [65]. These finding support the hypothesis that RSV is able to infect and to persist in the respiratory system. In the meantime this was also translated back into clinical studies that showed that persistent RSV detection in patients with COPD is associated with airway inflammation and accelerated decline in forced expiratory volume in 1 s (FEV_1). WILKINSON *et al.* [50] investigated a total of 241 sputum samples from 74 patients with COPD. RSV was detected in 32.8% of these sputum samples. Patients in whom RSV was more frequently detected (>50% of samples RSV PCR positive) had higher airway inflammation and faster FEV_1 decline over the study, independent of smoking status, exacerbation frequency and lower airway bacterial load. As far as other respiratory RNA viruses are concerned, it has been shown for human rhinoviruses that they can still be detected in 44% of children 6 weeks after an asthma exacerbation and in 25% as long as 6 months after the initial infection [66]. Asymptomatic carriage of rhinovirus has been reported in young children. It seemed that this was related to low viral loads [67]. However, comparable data in adults and particularly data in COPD patients are still lacking. It has been reported in a case–control study that rhinoviruses are detectable during stable disease in 5% of patients [37]. More data are available for adenoviruses; DNA viruses that are able to integrate into the host genome. 20 years ago PCR analysis showed that lung tissue from COPD patients contains more adenoviral E1A DNA than lung tissue from matched non-COPD smokers [68]. Some year's later E1A protein was found to be expressed in airway and alveolar epithelial cells from COPD patients [69]. Subsequent research demonstrated increased inflammation in E1A-transfected cells

[70, 71], as well as in a guinea pig model of latent adenoviral infection [72]. A comprehensive review of these and many additional studies on the role of respiratory adenoviral infection has been published recently [73]. However, later reports indicate that adenovirus E1A DNA is infrequently detected in respiratory secretions from patients with COPD [74].

Conclusions

The advent of more sensitive molecular detection methods, in particular, as well as the development of experimental infection models has progressed the understanding of respiratory viral infection during AECOPD. Research in this field remains a challenge due to the great diversity and number of respiratory viruses. In many cases the exact mechanisms of how respiratory viruses trigger AECOPD and what role they play in stable COPD are still not precisely defined. Rhinoviruses are the most prevalent and most investigated respiratory viruses in COPD. Influenza and RSV also play important roles, but more research is needed to better understand their roles. New respiratory viruses emerged recently but they do not seem to play a more important role than the well-known viruses. However, we have also seen the emergence of highly pathogenic new viruses with pandemic potential. This warrants ongoing surveillance, as well as increased research into the pathomechanisms of respiratory viral infection.

Statement of Interest
None declared.

References

1. Monto AS, Ullman BM. Acute respiratory illness in an American community. The Tecumseh study. *JAMA* 1974; 227: 164–169.
2. Makela MJ, Puhakka T, Ruuskanen O, *et al.* Viruses and bacteria in the etiology of the common cold. *J Clin Microbiol* 1998; 36: 539–542.
3. Creer DD, Dilworth JP, Gillespie SH, *et al.* Aetiological role of viral and bacterial infections in acute adult lower respiratory tract infection (LRTI) in primary care. *Thorax* 2006; 61: 75–79.
4. Heikkinen T, Jarvinen A. The common cold. *Lancet* 2003; 361: 51–59.
5. Arruda E, Pitkaranta A, Witek TJ Jr, *et al.* Frequency and natural history of rhinovirus infections in adults during autumn. *J Clin Microbiol* 1997; 35: 2864–2868.
6. Clark NM, Lynch JP 3rd. Influenza: epidemiology, clinical features, therapy, and prevention. *Semin Respir Crit Care Med* 2011; 32: 373–392.
7. Upshur RE, Moineddin R, Crighton EJ, *et al.* Interactions of viral pathogens on hospital admissions for pneumonia, croup and chronic obstructive pulmonary diseases: results of a multivariate time-series analysis. *Epidemiol Infect* 2006; 134: 1–5.
8. Denny FW Jr. The clinical impact of human respiratory virus infections. *Am J Respir Crit Care Med* 1995; 152: S4–S12.
9. Rohde G. Influenza A. Prevention and treatment. *Hot Topics Respir Med* 2010; 5: 23–29.
10. Gwaltney JM Jr, Moskalski PB, Hendley JO. Hand-to-hand transmission of rhinovirus colds. *Ann Intern Med* 1978; 88: 463–467.
11. Dick EC, Jennings LC, Mink KA, *et al.* Aerosol transmission of rhinovirus colds. *J Infect Dis* 1987; 156: 442–448.
12. Harris JM, Gwaltney JM Jr. Incubation periods of experimental rhinovirus infection and illness. *Clin Infect Dis* 1996; 23: 1287–1290.
13. Hendley JO, Gwaltney JM Jr. Mechanisms of transmission of rhinovirus infections. *Epidemiol Rev* 1988; 10: 243–258.
14. Drosten C, Gunther S, Preiser W, *et al.* Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med* 2003; 348: 1967–1976.
15. Van der Hoek L, Pyrc K, Jebbink MF, *et al.* Identification of a new human coronavirus. *Nat Med* 2004; 10: 368–373.
16. Zaki AM, van Boheemen S, Bestebroer TM, *et al.* Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med* 2012; 367: 1814–1820.
17. Walsh EE. Respiratory syncytial virus infection in adults. *Semin Respir Crit Care Med* 2011; 32: 423–432.
18. van den Hoogen BG, de Jong JC, Groen J, *et al.* A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001; 7: 719–724.
19. Rohde G, Borg I, Arinir U, *et al.* Relevance of human metapneumovirus in exacerbations of COPD. *Respir Res* 2005; 6: 150.
20. Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet* 2003; 362: 1733–1745.
21. Sullivan SJ, Jacobson RM, Dowdle WR, *et al.* 2009 H1N1 influenza. *Mayo Clin Proc* 2010; 85: 64–76.

22. Staunton DE, Merluzzi VJ, Rothlein R, *et al.* A cell adhesion molecule, ICAM-1, is the major surface receptor for rhinoviruses. *Cell* 1989; 56: 849–853.
23. Hofer F, Gruenberger M, Kowalski H, *et al.* Members of the low density lipoprotein receptor family mediate cell entry of a minor-group common cold virus. *Proc Natl Acad Sci USA* 1994; 91: 1839–1842.
24. Hofmann H, Pyrc K, Van Der HL, *et al.* Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proc Natl Acad Sci USA* 2005; 102: 7988–7993.
25. Segerman A, Atkinson JP, Marttila M, *et al.* Adenovirus type 11 uses CD46 as a cellular receptor. *J Virol* 2003; 77: 9183–9191.
26. Bergelson JM, Cunningham JA, Droguett G, *et al.* Isolation of a common receptor for Coxsackie B viruses and adenoviruses 2 and 5. *Science* 1997; 275: 1320–1323.
27. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 117: Suppl. 2, 380S–385S.
28. Jenkins CR, Celli B, Anderson JA, *et al.* Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J* 2012; 39: 38–45.
29. Yap FH, Ho PL, Lam KF, *et al.* Excess hospital admissions for pneumonia, chronic obstructive pulmonary disease, and heart failure during influenza seasons in Hong Kong. *J Med Virol* 2004; 73: 617–623.
30. Smith CB, Golden CA, Kanner RE, *et al.* Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. *Am Rev Respir Dis* 1980; 121: 225–232.
31. Gump DW, Phillips CA, Forsyth BR, *et al.* Role of infection in chronic bronchitis. *Am Rev Respir Dis* 1976; 113: 465–474.
32. Buscho RO, Saxtan D, Shultz PS, *et al.* Infections with viruses and *Mycoplasma pneumoniae* during exacerbations of chronic bronchitis. *J Infect Dis* 1978; 137: 377–383.
33. Ireland DC, Kent J, Nicholson KG. Improved detection of rhinoviruses in nasal and throat swabs by seminested RT-PCR. *J Med Virol* 1993; 40: 96–101.
34. Johnston SL, Sanderson G, Pattemore PK, *et al.* Use of polymerase chain reaction for diagnosis of picornavirus infection in subjects with and without respiratory symptoms. *J Clin Microbiol* 1993; 31: 111–117.
35. Johnston SL, Pattemore PK, Sanderson G, *et al.* Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995; 310: 1225–1229.
36. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
37. Rohde G, Wiethege A, Borg I, *et al.* Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalization – a case-control study. *Thorax* 2003; 58: 37–42.
38. Bandi V, Jakubowycz M, Kinyon C, *et al.* Infectious exacerbations of chronic obstructive pulmonary disease associated with respiratory viruses and non-typeable Haemophilus influenzae. *FEMS Immunol Med Microbiol* 2003; 37: 69–75.
39. Beckham JD, Cadena A, Lin J, *et al.* Respiratory viral infections in patients with chronic, obstructive pulmonary disease. *J Infect* 2005; 50: 322–330.
40. Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
41. Cameron RJ, de WD, Welsh TN, *et al.* Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med* 2006; 32: 1022–1029.
42. McManus TE, Marley AM, Baxter N, *et al.* Respiratory viral infection in exacerbations of COPD. *Respir Med* 2008; 102: 1575–1580.
43. Seemungal TAR, Harper-Owen R, Bhowmik A, *et al.* Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 2000; 16: 677–683.
44. Ko FW, Ip M, Chan PK, *et al.* Viral etiology of acute exacerbations of chronic obstructive pulmonary disease in Hong Kong. *Chest* 2007; 132: 900–908.
45. Walsh EE, Falsey AR, Hennessey PA. Respiratory syncytial and other virus infections in persons with chronic cardiopulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 791–795.
46. Hutchinson AF, Ghimire AK, Thompson MA, *et al.* A community-based, time-matched, case-control study of respiratory viruses and exacerbations of COPD. *Respir Med* 2007; 101: 2472–2481.
47. De Serres G, Lampron N, La Forge J, *et al.* Importance of viral and bacterial infections in chronic obstructive pulmonary disease exacerbations. *J Clin Virol* 2009; 46: 129–133.
48. Falsey AR, Formica MA, Hennessey PA, *et al.* Detection of respiratory syncytial virus in adults with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 639–643.
49. Borg I, Rohde G, Loseke S, *et al.* Evaluation of a quantitative real-time PCR for the detection of respiratory syncytial virus in pulmonary diseases. *Eur Respir J* 2003; 21: 944–951.
50. Wilkinson TM, Donaldson GC, Johnston SL, *et al.* Respiratory syncytial virus, airway inflammation and FEV_1 decline in patients with COPD. *Am J Respir Crit Care Med* 2006; 173: 871–876.
51. Hobson L, Everard ML. Persistent of respiratory syncytial virus in human dendritic cells and influence of nitric oxide. *Clin Exp Immunol* 2008; 15: 359–366.
52. Sikkel MB, Quint JK, Mallia P, *et al.* Respiratory syncytial virus persistence in chronic obstructive pulmonary disease. *Pediatr Infect Dis J* 2008; 27: Suppl. 10, S63–S70.

53. Mohan A, Chandra S, Agarwal D, *et al.* Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. *Respirology* 2010; 15: 536–542.
54. Rohde G, Borg I, Arinir U, *et al.* Evaluation of a real-time polymerase-chain reaction for severe acute respiratory syndrome (SARS) associated coronavirus in patients with hospitalised exacerbation of COPD. *Eur J Med Res* 2004; 9: 505–509.
55. Allander T, Tammi MT, Eriksson M, *et al.* Cloning of a human parvovirus by molecular screening of respiratory tract samples. *Proc Natl Acad Sci USA* 2005; 102: 12891–12896.
56. Manning A, Russell V, Eastick K, *et al.* Epidemiological profile and clinical associations of human bocavirus and other human parvoviruses. *J Infect Dis* 2006; 194: 1283–1290.
57. Ringshausen FC, Tan AY, Allander T, *et al.* Frequency and clinical relevance of human bocavirus infection in acute exacerbations of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 111–117.
58. Gaynor AM, Nissen MD, Whiley DM, *et al.* Identification of a novel polyomavirus from patients with acute respiratory tract infections. *PLoS Pathog* 2007; 3: e64.
59. Ringshausen FC, Heckmann M, Weissbrich B, *et al.* No evidence for WU polyomavirus infection in chronic obstructive pulmonary disease. *Infect Agent Cancer* 2009; 4: 12.
60. Abedi KB, Vallely PJ, Corless CE, *et al.* Age-related pattern of KI and WU polyomavirus infection. *J Clin Virol* 2008; 43: 123–125.
61. Rohde G, Borg I, Wiethege A, *et al.* Inflammatory response in acute viral exacerbations of COPD. *Infection* 2008; 36: 427–433.
62. Mallia P, Message SD, Gielen V, *et al.* Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med* 2011; 183: 734–742.
63. Borg I, Rohde G, Loeseke S, *et al.* Evaluation of a quantitative real-time PCR for the detection of RSV in pulmonary diseases. *Eur Respir J* 2003; 21: 944–951.
64. Schwarze J, O'Donnell DR, Rohwedder A, *et al.* Latency and persistence of respiratory syncytial virus despite T cell immunity. *Am J Respir Crit Care Med* 2004; 169: 801–805.
65. Boukhvalova MS, Prince GA, Blanco JC. Respiratory syncytial virus infects and abortively replicates in the lungs in spite of preexisting immunity. *J Virol* 2007; 81: 9443–9450.
66. Kling S, Donninger H, Williams Z, *et al.* Persistence of rhinovirus RNA after asthma exacerbation in children. *Clin Exp Allergy* 2005; 35: 672–678.
67. Jansen RR, Wieringa J, Koekkoek SM, *et al.* Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values. *J Clin Microbiol* 2011; 49: 2631–2636.
68. Matsuse T, Hayashi S, Kuwano K, *et al.* Latent adenoviral infection in the pathogenesis of chronic airways obstruction. *Am Rev Respir Dis* 1992; 146: 177–184.
69. Elliott WM, Hayashi S, Hogg JC. Immunodetection of adenoviral E1A proteins in human lung tissue. *Am J Respir Cell Mol Biol* 1995; 12: 642–648.
70. Keicho N, Elliott WM, Hogg JC, *et al.* Adenovirus E1A upregulates interleukin-8 expression induced by endotoxin in pulmonary epithelial cells. *Am J Physiol* 1997; 272: L1046–L1052.
71. Morimoto K, Gosselink J, Kartono A, *et al.* Adenovirus E1A regulates lung epithelial ICAM-1 expression by interacting with transcriptional regulators at its promoter. *Am J Physiol Lung Cell Mol Physiol* 2009; 296: L361–L371.
72. Vitalis TZ, Kern I, Croome A, *et al.* The effect of latent adenovirus 5 infection on cigarette smoke-induced lung inflammation. *Eur Respir J* 1998; 11: 664–669.
73. Hayashi S, Hogg JC. Adenovirus infections and lung disease. *Curr Opin Pharmacol* 2007; 7: 237–243.
74. McManus TE, Marley AM, Baxter N, *et al.* Acute and latent adenovirus in COPD. *Respir Med* 2007; 101: 2084–2090.

Chapter 8

Virus–bacteria interactions in COPD exacerbations

Patrick Mallia, Aran Singanayagam and Sebastian L. Johnston

SUMMARY: Chronic obstructive pulmonary disease (COPD) is a disease characterised by acute exacerbations. Respiratory infections, including viruses and bacteria, are common aetiological agents and some studies have detected dual viral–bacterial infection during exacerbations. However, the mechanisms underlying virus–bacteria interactions in COPD are poorly characterised. *In vitro* studies have shown that viral infection can increase susceptibility to secondary bacterial infection, and animal models of sequential infection have revealed potential molecular mechanisms of how viral infection may impact upon subsequent secondary bacterial infection. A recently reported human experimental rhinovirus infection model of COPD exacerbation has provided additional evidence that viral–bacterial co-infection may be more common in COPD exacerbations than previously thought. Further understanding of the mechanisms involved in virus–bacteria interactions may facilitate development of novel therapies with the potential to reduce or prevent secondary bacterial infections following respiratory viral exacerbations in COPD. In this chapter, the evidence for dual viral and bacterial infection in COPD exacerbations is outlined, and existing evidence for underlying mechanistic interactions is discussed.

KEYWORDS: Bacteria, chronic obstructive pulmonary disease, exacerbations, rhinoviruses, viruses

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Eur Respir Monogr 2013; 60: 76–83.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017612
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Chronic obstructive pulmonary disease (COPD) is predicted to be the fourth most common cause of death worldwide by 2030. COPD is characterised by poorly reversible lung function, airway inflammation, impaired health status and a progressive clinical decline. The chronic clinical course of the disease is punctuated by the occurrence of acute exacerbations that become more common as the disease progresses. Acute exacerbations are associated with accelerated loss of lung function, impaired quality of life, significant mortality and excess healthcare costs. Therefore, preventing exacerbations is a major therapeutic goal that has not been adequately achieved with currently available treatments. The major causes of exacerbations are respiratory infections, with

both viruses and bacteria commonly detected in exacerbations. As both viral and bacterial infections are common, it is likely that dual viral–bacterial infection will occur commonly and *in vitro* models have shown that viral infection can increase susceptibility to bacterial infection. However, reported rates of dual infection in COPD exacerbations have generally been low. Recent data from an experimental rhinovirus infection model of COPD exacerbation has provided new evidence that viral–bacterial co-infection may be more common than previously thought in COPD exacerbations. This should provide a new impetus for the development of antiviral therapies with the potential to reduce or prevent secondary bacterial infections as novel treatments for COPD exacerbations.

Infection and COPD exacerbations

Bacterial infection has long been considered the main cause of COPD exacerbations. Numerous studies have reported high rates of bacterial infection in samples collected during exacerbations, but bacteria can also be present in stable COPD patients [1]. Studies comparing rates of bacterial detection in stable and exacerbated patients have generally reported higher infection rates in exacerbations, providing evidence for a role of bacteria in exacerbations [1–4]. The most common bacteria detected in COPD exacerbations are Haemophilus influenzae, Moraxella catarrhalis and Streptococcus pneumoniae. The perceived role of bacteria in COPD exacerbations has underpinned the use of antibiotics as a mainstay of treatment; however, the therapeutic effect of antibiotics and the role of bacteria in COPD exacerbations continue to be debated [5].

The greater frequency of exacerbations in the winter months [6] and the occurrence of upper respiratory symptoms preceding exacerbations suggest a link between respiratory viral infections and COPD exacerbations [7]. Older studies investigating the role of viruses in COPD exacerbations reported virus detection rates of ~10–20% during exacerbations [8, 9], casting doubt on the importance of the role of viral infection. However, the diagnostic methods used in these studies had low sensitivities for virus detection, especially for rhinoviruses, which are the commonest cause of viral upper respiratory tract infections. The application of molecular diagnostic techniques such as PCR led to a re-evaluation of the role of viruses in COPD exacerbations. Studies using PCR have detected viruses in up to 47–56% of exacerbations [1, 10–13], with picornaviruses (predominantly rhinoviruses) the most frequently detected viruses [14]. However, the role of viral infection in COPD exacerbations continues to be debated as PCR can detect small amounts of viral nucleic acid and therefore does not definitively prove the presence of live viruses. However, it is equally possible that the role of viral infections in COPD exacerbations has been underestimated as patients are evaluated at the time of presentation, which may occur considerably later than the initial viral infection. As rapid diagnostic methods and antiviral agents become available the relationship between viral infections and COPD will no longer be of just academic interest, but will have potential therapeutic implications and therefore warrants further study.

Virus–bacterial interactions

In vitro studies

Viral and bacterial infections can modulate host immunity and thereby alter immune responses to subsequent infections. It is well established that influenza infection can impair host antibacterial immune responses and this can result in secondary bacterial pneumonia [15, 16], predominantly with *S. pneumoniae* but also *Staphylococcus aureus* and *H. influenzae*. Influenza infection of respiratory epithelial cells results in phenotypic changes in cells that may promote the adherence of bacterial pathogens *via* a number of possible mechanisms, such as the promotion of bacterial adherence and internalisation to epithelial cells by viral neuraminidase [15, 17].

Much less is known about the effects of other respiratory viruses, such as rhinoviruses, on bacterial infection. There is evidence that rhinovirus infection increases bacterial cellular adherence in

in vitro models. Rhinovirus infection of nasal epithelial cells results in increased adherence of *S. pneumoniae*, *S. aureus* and *H. influenzae* [18], and also increases adherence of *S. pneumoniae* to human tracheal epithelial cells [19]. Rhinovirus infection upregulates the expression of several surface molecules, including fibronectin, platelet activating factor receptor and carcinoembryonic antigen-related cell adhesion molecule (CEACAM), which mediate bacterial adherence to cells. In addition, rhinovirus infection promotes internalisation of *S. aureus* into epithelial cells [20]. Another mechanism whereby rhinovirus infection may predispose to secondary bacterial infections is disruption of the airway epithelial barrier function. Rhinovirus infection *in vitro* reduces transepithelial resistance, induces tight junction breakdown and facilitates bacterial transmigration across polarised airway epithelial cells [21, 22]. In addition to effects on epithelial cells, rhinovirus infection of macrophages impairs their responses to bacterial products (fig. 1) [23]. Most research has focussed on primary viral infection and secondary bacterial infection but one study has suggested that bacterial infection can also influence immune responses to viral infection, as infection of epithelial cells by *H. influenzae* increases susceptibility to infection by rhinovirus, possibly by upregulation of intracellular adhesion molecule (ICAM)-1 [24].

In vitro studies have highlighted a number of mechanisms whereby rhinovirus infection may increase susceptibility to bacterial infection, but it is not known whether these are relevant *in vivo*. Biopsy studies have revealed that in human rhinovirus infections very few epithelial cells are actually infected and, unlike influenza, there is minimal cytopathic effect [25]. The pathological features and symptoms of infection result from the host inflammatory response to rhinovirus infection. Therefore, the relevance of *in vitro* models to *in vivo* infection is debatable.

Animal models

Although there are some existing studies that have used animal models of COPD to investigate mechanisms of single-agent infection with viruses or bacteria [26–30], there are no animal studies that have combined models of COPD and dual viral–bacterial infection. There are studies using

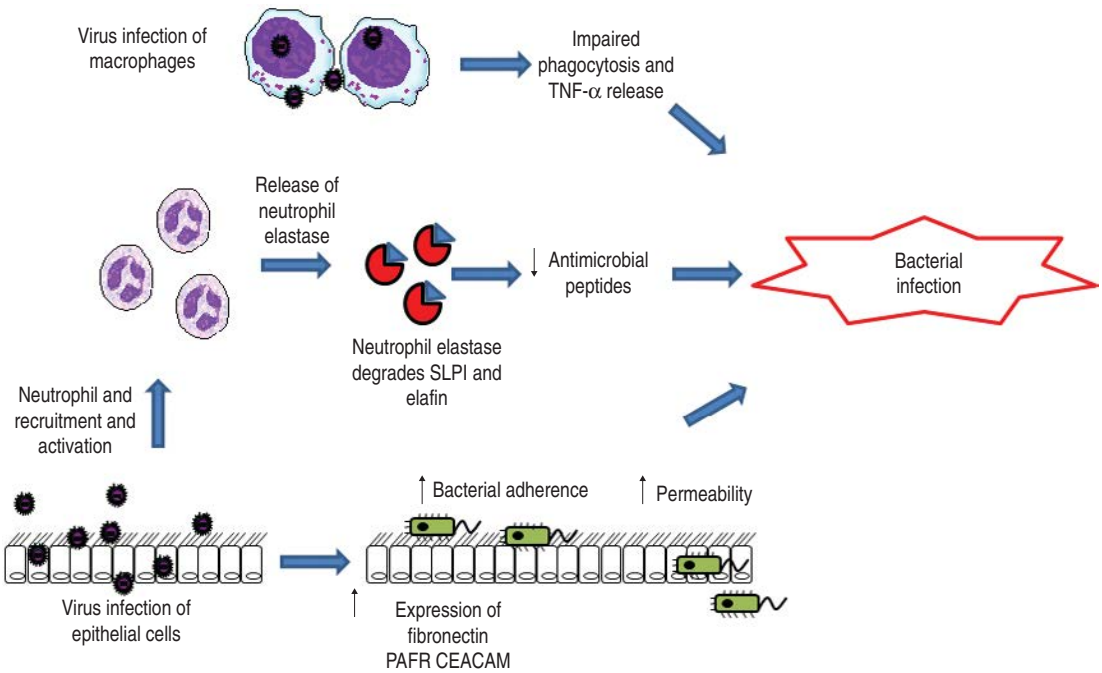

Figure 1. Potential mechanisms of secondary bacterial infection following virus infection of the respiratory tract. TNF-α: tumour necrosis factor-α; SLPI: secretory leukoprotease inhibitor; PAFR: platelet activating factor receptor; CEACAM: carcinoembryonic antigen-related cell adhesion molecule.

animal models of sequential viral and bacterial infection to investigate molecular mechanisms of how respiratory viruses such as influenza or rhinoviruses may impact upon subsequent secondary bacterial infection and these suggest a range of underlying mechanisms, which may be of relevance in COPD.

Several studies have demonstrated that the Type I interferon (IFN) signalling pathway plays a key role in mediating development of post-influenza bacterial pneumonia in mice. SHAHANGIAN *et al.* [31] showed that influenza-infected mice deficient for Type I IFN-α/β receptor signalling (*IFNAR*$^{-/-}$) have improved survival and clearance of secondary *S. pneumoniae* infection compared to wild-type controls. The authors concluded that Type I IFN induced during influenza infection in the lung may play a role in sensitising the host to bacterial infections in the post-influenza period. LI *et al.* [32] similarly showed that *IFNAR*$^{-/-}$ mice infected with influenza manifest increased neutrophil recruitment and increased expression of interleukin (IL)-17, and clear secondary bacterial infection more effectively from their lungs. Since lung γδT-cells produce the majority of IL-17, the authors carried out further adoptive transfer experiments, in which γδ cells were transferred from *IFNAR*$^{-/-}$ mice to wild-type mice and this led to reduced susceptibility to secondary *S. pneumoniae* infection [32]. NAKAMURA *et al.* [33] used a mouse model of co-infection of the upper respiratory tract with influenza and *S. pneumoniae* to show that pneumococcal colonisation followed by influenza co-infection resulted in increased lung pneumococcal loads at day 7 and synergistically increased Type I IFN induction compared to mice infected with *S. pneumoniae* or influenza virus alone. *IFNAR*$^{-/-}$ mice did not show such an increase.

Other animal studies have implicated impaired macrophage and neutrophil responses [34–37], Type II IFN-γ signalling [38], viral neuramidase [39] and upregulation of IL-10 [40] or platelet activating factor [41] in promoting post-influenza secondary bacterial pneumonia. It is likely that there is a complex interplay between a number of immune responses involved in virus–bacteria interactions and further animal model studies, using relevant transgenic strains and/or exogenous administration of recombinant proteins or blocking antibodies, will allow direct testing of cause and effect, and further facilitate our understanding of this important subject.

Although a number of studies have assessed virus–bacteria interactions using influenza in mouse models, very few studies have focussed on rhinoviruses, which are a more frequent cause of exacerbations in COPD. UNGER *et al.* [42] used a mouse co-infection model of rhinovirus and *H. influenzae* and showed delayed bacterial clearance in dual-infected animals compared to mice infected with bacteria alone. This was associated with attenuation of expression of the neutrophil chemokines macrophage inflammatory protein (MIP)-2 and keratinocyte chemoattractant (KC), and impaired neutrophil recruitment in response to the bacterial challenge. The authors propose that reduced neutrophil recruitment compromises the ability of the lungs to clear bacteria and thus promotes bacterial persistence.

Although these studies shed light on how the respiratory viral infection may alter the course and severity of a secondary bacterial infection, they do not provide direct mechanistic information about whether and, if so, how viral infections can directly trigger secondary bacterial infection, since both the viral and bacterial trigger are introduced artificially and therefore one infection does not directly trigger the second. The only animal model study that has attempted to investigate this was recently reported by GOULDING *et al.* [43]. They evaluated the effect of influenza infection on the lower respiratory microbiota in mice at day 7 post-infection and showed that influenza caused a dysbiosis with concentration into two dominant communities predominantly containing *Acinetobacter*, *Staphylococcus*, *Prevotella*, *Moraxella* and *Proteus mirabilis* species. This study provides direct evidence that a primary virus infection can directly alter the lower respiratory tract microbiota, but the relevance of this disturbance to development of secondary bacterial infection is unclear and the underlying mechanisms remain uncharacterised. Further studies are now warranted.

The relevance of existing animal model studies to virus–bacteria interactions in chronic lung diseases such as COPD is unclear, given that there is some evidence that IFN induction by rhinoviruses may be deficient in patients with COPD and asthma, and data from some of the

studies discussed above would suggest that this would have a beneficial impact on secondary bacterial infection [44, 45]. COPD is frequently characterised by bacterial colonisation of the lower airways and the impact of virus infection on this pre-existing colonisation in bronchitic/emphysematous lungs is unclear. Future studies should aim to further evaluate the effect of viral infection on the lower respiratory microbiome using validated animal models of COPD to assess whether a primary viral infection can alter the bacterial flora and thus increase the risk of secondary bacterial infection.

Clinical studies of dual infection in COPD

Both bacterial and viral infections are common in COPD exacerbations, but few studies have examined the role of co-infection in COPD exacerbations. The studies that are available have detected dual infection in a minority of exacerbations ranging from <10% to, at most, 25% [1, 46–48]. Therefore, it would appear that dual viral–bacterial infection appears not to play a major role in COPD exacerbations. However, in these studies, samples were collected only at a single time during the exacerbation. If viral and bacterial infections occur consecutively, it is likely that the period of time during which both are detectable concurrently may be relatively short, and therefore the true prevalence of dual infection will be underestimated with only a single sampling time-point. The only study that collected samples on two occasions during exacerbations suggested that this may in fact be the case. HUTCHINSON *et al.* [49] sampled patients at the onset of exacerbation and again 5–7 days later, and found that 36% of exacerbations in which a virus was detected at onset developed secondary bacterial infection, a further 71% of patients with bacterial exacerbations had reported symptoms of a viral upper respiratory tract infection prior to onset so the true association may be even higher. Determining the role of dual infection in COPD exacerbations is clearly difficult in naturally occurring exacerbations due to variation in time to presentation, the effects of treatment and the difficulty in collecting multiple clinical samples in acutely unwell patients.

Experimental rhinovirus infection in COPD

We have developed a human model of COPD exacerbation using experimental rhinovirus infection. Inoculation of COPD subjects with rhinovirus induced the typical symptomatic, physiological and inflammatory features of a COPD exacerbation [50, 51]. We then used this model to study virus/bacterial interactions in COPD as it overcomes many of the difficulties described previously that are problematic to resolve with naturally occurring exacerbations. As the time of onset of exacerbation is known, samples can be collected at pre-determined time-points, thus removing any variability in time to presentation; multiple samples can be collected during the course of the exacerbation and treatment can be withheld. Therefore, the rhinovirus infection model is ideal for examining the relationships between virus and bacterial infection in COPD. Following rhinovirus infection, we found that 60% of the COPD patients developed secondary bacterial infections, predominantly *S. pneumoniae* and *H. influenzae* [51]. Bacterial infection was not seen in non-obstructed smokers and nonsmokers also inoculated with rhinovirus. Moreover, there was a temporal sequence of rhinovirus infection occurring first with a peak in virus load on day 5–9 post-inoculation, followed by bacterial infection that peaked on day 15 post-inoculation. The incidence of secondary bacterial infection was related to high levels of the protease neutrophil elastase and deficiencies in the antimicrobial peptides secretory leukocyte protease inhibitor (SLPI) and elafin. These results suggest that dual infection in COPD exacerbations may be much more common than is suggested from the studies of naturally occurring exacerbations. Our data also suggest that viral and bacterial infections occur sequentially and, therefore, collecting samples at a single time-point during an exacerbation will underestimate the true prevalence of dual infection.

Therapeutic implications

Current therapy for COPD exacerbations consists of supportive treatments (controlled oxygen therapy and nebulised bronchodilators), together with corticosteroids and antibiotics. Corticosteroids

have been shown to improve outcomes overall in COPD exacerbations but recent data have suggested that in some patients, corticosteroids may have adverse effects [52]. The role of antibiotics is also controversial, with some studies showing no effect and others showing clinical benefit [53]. A study using procalcitonin as a marker of bacterial infection found that antibiotic use could be reduced from 72% of exacerbations to 40% with no difference in outcomes [54]. Therefore, it is likely that antibiotics are overprescribed in COPD exacerbations and this may be due to use of antibiotics in viral exacerbations. The data from our experimental rhinovirus infection studies strongly implicates virus infection as a cause of exacerbations (>90% of virus-infected COPD subjects developed exacerbations [44, 50]) and also as an important factor contributing to bacterial infections in COPD exacerbations [51]. Therefore, treatment of viral infections may not only prevent viral exacerbations but may also have an impact on preventing secondary bacterial exacerbations. Currently, there are no drugs licensed for treatment of rhinovirus infections. A capsid binding inhibitor (pleconaril) was developed for treatment of rhinovirus infections and was shown to have clinical efficacy [55], but was not approved for use as a treatment for the common cold. There have been no trials of pleconaril in COPD so it is not known whether it is effective in treating rhinovirus-induced COPD exacerbations. Other drugs for the treatment of rhinovirus infections are in development and trials of antiviral agents in COPD are awaited. It will be particularly important to determine whether treatment of a rhinovirus infection in COPD subjects can prevent secondary bacterial infection, as such a result would lead to a paradigm shift in terms of treatment/prevention of COPD exacerbations.

A number of *in vitro* studies have suggested other treatments that may be of benefit in viral and bacterial infections and, therefore, may be potential treatments for COPD exacerbations. The antihistamine levocetirizine reduced adhesion of *S. aureus* and *H. influenzae* to primary human nasal epithelial cells, probably by reducing expression of fibronectin and CEACAM [56], and similar effects were seen with the macrolide clarithromycin [57]. Studies have suggested that macrolides can reduce both colds [58] and COPD exacerbations [59] in clinical trials. Macrolides have antibacterial, antiviral [60] and anti-inflammatory effects, and all these mechanisms may be important in reducing COPD exacerbations.

Conclusions

COPD exacerbations are a major cause of morbidity and mortality and new treatments are urgently required. Virus and bacterial infections are the main causes of exacerbations and, although dual infection has not been commonly detected, evidence from *in vitro* studies and experimental rhinovirus infections suggests this may be more common than was previously thought. Antiviral agents and drugs that reduce bacterial adherence have potential as new treatments for COPD exacerbations.

Statement of Interest

S.L. Johnston has received fees for attending a symposium, fees for speaking and research funding from Asthma UK, the Biomedical Research Centre, the British Medical Association, the British Lung Foundation, the European Academy of Allergy and Clinical Immunology, the European Research Council, the European Respiratory Society, EU ERC MoRIAE, Imperial College Healthcare NHS Trust, the Medical Research Council, the Moulton Foundation, the National Institute for Health Research, University of Leicester, the Wellcome Trust Grant for the Centre for Respiratory Infection, AstraZeneca, Centocor, Pfizer, Sanofi Pasteur and Synairgen. S.L. Johnston is a shareholder of Synairgen, and has received fees for consultancy from AstraZeneca, Centocor, Sanofi-Pasteur, Synairgen, Grunenthal, Boehringer Ingelheim, Novartis, Chiesi and GSK.

References

1. Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.

2. Wilkinson TM, Hurst JR, Perera WR, *et al.* Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD. *Chest* 2006; 129: 317–324.
3. Hurst JR, Perera WR, Wilkinson TM, *et al.* Systemic and upper and lower airway inflammation at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 71–78.
4. Rosell A, Monso E, Soler N, *et al.* Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med* 2005; 165: 891–897.
5. Boersma WG. Antibiotics in acute exacerbations of COPD: the good, the bad and the ugly. *Eur Respir J* 2012; 40: 1–3.
6. Jenkins CR, Celli B, Anderson JA, *et al.* Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *Eur Respir J* 2012; 39: 38–45.
7. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
8. Smith CB, Golden CA, Kanner RE, *et al.* Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. *Am Rev Respir Dis* 1980; 121: 225–232.
9. Buscho RO, Saxtan D, Shultz PS, *et al.* Infections with viruses and *Mycoplasma pneumoniae* during exacerbations of chronic bronchitis. *J Infect Dis* 1978; 137: 377–383.
10. Rohde G, Wiethege A, Borg I, *et al.* Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; 58: 37–42.
11. Qiu Y, Zhu J, Bandi V, *et al.* Biopsy neutrophilia, neutrophil chemokine and receptor gene expression in severe exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2003; 168: 968–975.
12. Tan WC, Xiang X, Qiu D, *et al.* Epidemiology of respiratory viruses in patients hospitalized with near-fatal asthma, acute exacerbations of asthma, or chronic obstructive pulmonary disease. *Am J Med* 2003; 115: 272–277.
13. Cameron RJ, de Wit D, Welsh TN, *et al.* Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Int Care Med* 2006; 32: 1022–1029.
14. Mohan A, Chandra S, Agarwal D, *et al.* Prevalence of viral infection detected by PCR and RT-PCR in patients with acute exacerbation of COPD: a systematic review. *Respirology* 2010; 15: 536–542.
15. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin Microbiol Rev* 2006; 19: 571–582.
16. Hussell T, Cavanagh MM. The innate immune rheostat: influence on lung inflammatory disease and secondary bacterial pneumonia. *Biochem Soc Trans* 2009; 37: 811–813.
17. Passariello C, Nencioni L, Sgarbanti R, *et al.* Viral hemagglutinin is involved in promoting the internalisation of *Staphylococcus aureus* into human pneumocytes during influenza A H1N1 virus infection. *Int J Med Microbiol* 2011; 301: 97–104.
18. Wang JH, Kwon HW, Jang YJ. Rhinovirus enhances various bacterial adhesions to nasal epithelial cells simultaneously. *Laryngoscope* 2009; 119: 1406–1411.
19. Ishizuka S, Yamaya M, Suzuki T, *et al.* Effects of rhinovirus infection on the adherence of *Streptococcus pneumoniae* to cultured human airway epithelial cells. *J Infect Dis* 2003; 188: 1928–1939.
20. Passariello C, Schippa S, Conti C, *et al.* Rhinoviruses promote internalisation of *Staphylococcus aureus* into non-fully permissive cultured pneumocytes. *Microbes Infection* 2006; 8: 758–766.
21. Comstock AT, Ganesan S, Chattoraj A, *et al.* Rhinovirus-induced barrier dysfunction in polarized airway epithelial cells is mediated by NADPH oxidase 1. *J Virol* 2011; 85: 6795–6808.
22. Sajjan U, Wang Q, Zhao Y, *et al.* Rhinovirus disrupts the barrier function of polarized airway epithelial cells. *Am J Respir Crit Care Med* 2008; 178: 1271–1281.
23. Oliver BG, Lim S, Wark P, *et al.* Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. *Thorax* 2008; 63: 519–525.
24. Sajjan US, Jia Y, Newcomb DC, *et al.* H. influenzae potentiates airway epithelial cell responses to rhinovirus by increasing ICAM-1 and TLR3 expression. *FASEB J* 2006; 20: 2121–2123.
25. Mosser AG, Brockman-Schneider R, Amineva S, *et al.* Similar frequency of rhinovirus-infectible cells in upper and lower airway epithelium. *J Infect Dis* 2002; 185: 734–743.
26. Sajjan U, Ganesan S, Comstock AT, *et al.* Elastase- and LPS-exposed mice display altered responses to rhinovirus infection. *Am J Physiol Lung Cell Mol Physiol* 2009; 297: L931–L944.
27. Ganesan S, Faris AN, Comstock AT, *et al.* Elastase/LPS-exposed mice exhibit impaired innate immune responses to bacterial challenge: role of scavenger receptor A. *Am J Pathol* 2012; 180: 61–72.
28. Pang B, Hong W, West-Barnette SL, *et al.* Diminished ICAM-1 expression and impaired pulmonary clearance of nontypeable *Haemophilus influenzae* in a mouse model of chronic obstructive pulmonary disease/emphysema. *Infect Immun* 2008; 76: 4959–4967.
29. Wang D, Wang Y, Liu YN. Experimental pulmonary infection and colonization of *Haemophilus influenzae* in emphysematous hamsters. *Pulm Pharmacol Ther* 2010; 23: 292–299.
30. Inoue S, Nakamura H, Otake K, *et al.* Impaired pulmonary inflammatory responses are a prominent feature of streptococcal pneumonia in mice with experimental emphysema. *Am J Respir Crit Care Med* 2003; 167: 764–770.
31. Shahangian A, Chow EK, Tian X, *et al.* Type I IFNs mediate development of postinfluenza bacterial pneumonia in mice. *J Clin Invest* 2009; 119: 1910–1920.

32. Li W, Moltedo B, Moran TM. Type I interferon induction during influenza virus infection increases susceptibility to secondary *Streptococcus pneumoniae* infection by negative regulation of γδT cells. *J Virol* 2012; 86: 12304–12312.
33. Nakamura S, Davis KM, Weiser JN. Synergistic stimulation of type I interferons during influenza virus coinfection promotes *Streptococcus pneumoniae* colonization in mice. *J Clin Invest* 2011; 121: 3657–3665.
34. Jakab GJ. Immune impairment of alveolar macrophage phagocytosis during influenza virus pneumonia. *Am Rev Respir Dis* 1982; 126: 778–782.
35. McNamee LA, Harmsen AG. Both influenza-induced neutrophil dysfunction and neutrophil-independent mechanisms contribute to increased susceptibility to a secondary *Streptococcus pneumoniae* infection. *Infect Immun* 2006; 74: 6707–6721.
36. Nickerson CL, Jakab GJ. Pulmonary antibacterial defenses during mild and severe influenza virus infection. *Infect Immun* 1990; 58: 2809–2814.
37. Jakab GJ, Warr GA, Knight ME. Pulmonary and systemic defenses against challenge with *Staphylococcus aureus* in mice with pneumonia due to influenza A virus. *J Infect Dis* 1979; 140: 105–108.
38. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-γ during recovery from influenza infection. *Nat Med* 2008; 14: 558–564.
39. McCullers JA, Bartmess KC. Role of neuraminidase in lethal synergism between influenza virus and *Streptococcus pneumoniae*. *J Infect Dis* 2003; 187: 1000–1009.
40. van der Sluijs KF, van Elden LJ, Nijhuis M, *et al.* IL-10 is an important mediator of the enhanced susceptibility to pneumococcal pneumonia after influenza infection. *J Immunol* 2004; 172: 7603–7609.
41. McCullers JA, Rehg JE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*: characterization of a mouse model and the role of platelet-activating factor receptor. *J Infect Dis* 2002; 186: 341–350.
42. Unger BL, Faris AN, Ganesan S, *et al.* Rhinovirus attenuates non-typeable *Hemophilus influenzae*-stimulated IL-8 responses *via* TLR2-dependent degradation of IRAK-1. *PLoS Pathog* 2012; 8: e1002969.
43. Goulding J, Godlee A, Vekaria S, *et al.* Lowering the threshold of lung innate immune cell activation alters susceptibility to secondary bacterial superinfection. *J Infect Dis* 2011; 204: 1086–1094.
44. Mallia P, Message SD, Gielen V, *et al.* Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med* 2011; 183: 734–742.
45. Contoli M, Message SD, Laza-Stanca V, *et al.* Role of deficient type III interferon λ production in asthma exacerbations. *Nat Med* 2006; 12: 1023–1026.
46. Kherad OL, Kaiser L, Bridevaux PO, *et al.* Upper-respiratory viral infection, biomarkers, and COPD exacerbations. *Chest* 2010; 138: 896–904.
47. Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662–671.
48. Bozinovski S, Hutchinson A, Thompson M, *et al.* Serum amyloid a is a biomarker of acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 269–278.
49. Hutchinson AF, Ghimire AK, Thompson MA, *et al.* A community-based, time-matched, case-control study of respiratory viruses and exacerbations of COPD. *Respir Med* 2007; 101: 2472–2481.
50. Mallia P, Message SD, Kebadze T, *et al.* An experimental model of rhinovirus induced chronic obstructive pulmonary disease exacerbations: a pilot study. *Respir Res* 2006; 7: 116.
51. Mallia PJ, Footitt Sotero R, Jepson AM, *et al.* Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in COPD. *Am J Respir Crit Care Med* 2012; 186: 1117–1124.
52. Bafadhel M, McKenna S, Terry S, *et al.* Blood eosinophils to direct corticosteroid treatment of exacerbations of COPD: a randomized placebo controlled trial. *Am J Respir Crit Care Med* 2012; 186: 48–55.
53. Vollenweider DJ, Jarrett H, Steurer-Stey CA, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 12: CD010257.
54. Stolz D, Christ-Crain M, Bingisser R, *et al.* Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest* 2007; 131: 9–19.
55. Hayden FG, Herrington DT, Coats TL, *et al.* Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials. *Clin Infect Dis* 2003; 36: 1523–1532.
56. Min JY, Shin SH, Kwon HJ, *et al.* Levocetirizine inhibits rhinovirus-induced bacterial adhesion to nasal epithelial cells through down-regulation of cell adhesion molecules. *Ann Allergy Asthma ImmunoL* 2012; 108: 44–48.
57. Wang JH, Lee SH, Kwon HJ, *et al.* Clarithromycin inhibits rhinovirus-induced bacterial adhesions to nasal epithelial cells. *Laryngoscope* 2010; 120: 193–199.
58. Suzuki T, Yanai M, Yamaya M, *et al.* Erythromycin and common cold in COPD. *Chest* 2001; 120: 730–733.
59. Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–698.
60. Gielen V, Johnston SL, Edwards MR. Azithromycin induces anti-viral responses in bronchial epithelial cells. *Eur Respir J* 2010; 36: 646–654.

Chapter 9

Impact of exacerbations in the natural course of COPD

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SUMMARY: Exacerbations represent an important event in the natural history of patients with chronic obstructive pulmonary disease (COPD). They are associated with considerable physiological deterioration and increased airway inflammatory changes, and may enhance disease progression by accelerating the decline in lung function. Some patients are prone to frequent exacerbations, which are an important cause of hospital admission and readmission, and these frequent episodes may have considerable impact on quality of life, activities of daily living and mortality. Although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype: the "frequent exacerbator".

KEYWORDS: Chronic obstructive pulmonary disease, exacerbation, inflammation, phenotype, quality of life

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Eur Respir Monogr 2013; 60: 84–95.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017712
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Chronic obstructive pulmonary disease (COPD) has traditionally been considered a lung disease characterised by a chronic, progressive and poorly reversible limitation of airflow. Since the seminal study by FLETCHER and PETO [1] in 1977, the natural history of the disease has been understood as an accelerated loss of lung function expressed as a decline in forced expiratory volume in 1 s (FEV_1). However, past decades have been characterised by a radical shift in the importance given to exacerbations, which are now considered crucial events in the natural history of the disease. This renewed interest began to take shape following several experiences emphasising the strong impact of exacerbations on local and systemic inflammation, progression of the disease, quality of life and prognosis of COPD patients.

The impact of COPD exacerbations on local and systemic inflammation

Inflammation is a key feature in the pathophysiology of COPD, as shown by the presence of activated neutrophils and macrophages and increased numbers of inflammatory mediators in the airways [2]. Exacerbations of COPD are generally considered to reflect a flare-up of these

underlying inflammatory processes, although there has been little information available on the nature of the inflammatory markers [3].

During exacerbations of COPD, an increase in airway inflammation has been noticed, as measured by increased sputum neutrophil and lymphocyte counts, increased sputum myeloperoxidase (MPO) and interleukin (IL)-8, and activation of nuclear factor (NF)-κB in sputum macrophages compared with the stable phase [4–8]. Neutrophils are attracted into the airway lumen during exacerbations and increased levels of neutrophils in sputum correlated with rapid decline in FEV1 [9]. Recent reports have also identified a significantly increased number of eosinophils in patients with COPD exacerbation, although the significance of these findings is not fully understood [5, 10].

Besides the abnormal local inflammatory response, systemic inflammation is also considered an important component of the disease process. Increased systemic inflammation during exacerbations of COPD is indicated by higher levels of some inflammatory markers in the blood. These include C-reactive protein (CRP), inflammatory cytokines and the neutrophil marker MPO [11–15]. An extensive evaluation of several biomarkers at COPD exacerbation has been published, from which CRP seems to be the most useful and selective [16]. In the presence of one or more recorded major exacerbation symptoms, CRP seems to be able to reliably differentiate exacerbation of COPD from day-to-day symptom variation. However, CRP or any other of the plasma analytes alone is neither sufficiently sensitive nor specific to be a useful biomarker in the absence of symptom assessment. An up-regulation of systemic inflammation during an exacerbation of COPD has been demonstrated by GROENEWEGEN *et al.* [17]; this finding was recently confirmed by a study indicating that mucus purulence and CRP, but not procalcitonin, are predictors of bacterial aetiology of COPD exacerbation [18]. Elevated levels of the systemic inflammatory markers IL-6, soluble tumour necrosis factor receptor p55 (sTNFR55), sTNFR75, soluble IL-1β receptor (sIL-1RII) and neutrophil bacterial/permeability-increasing protein (BPI) were detected on admission for exacerbation of COPD. During treatment, the authors noticed a rapid decrease in IL-6 and sTNFR75 whereas, in contrast, sTNFR55 and BPI remained elevated. Moreover, sIL-1RII and total antioxidant status increased during the first 8 days of treatment. In the stable condition, inflammatory markers returned to values comparable to those of healthy controls, with the exception of BPI, which remained persistently elevated in COPD patients.

Residual BPI elevation could be a signal of an alteration in the immunity response that persists over the exacerbation and could be responsible for COPD progression.

Plasma fibrinogen has also been studied in patients with stable COPD and during exacerbation [13, 19, 20]: in one of these studies, changes in plasma fibrinogen and frequency of exacerbations were evaluated during a 7-year period, and patients with frequent exacerbations showed an increase in plasma fibrinogen over time [19]. Patients with COPD seem to be more likely to have significantly decreased blood levels of osteoprotegerin and higher levels of CRP. Furthermore, sTNFR1 and osteoprotegerin changes are related to disease severity and frequency of exacerbations [21]. During exacerbations of COPD, compared with the stable phase, it has also been noted that there is a significant increase in urinary excretion of desmosine and isodesmosine (products of the degradation of lung elastin) coinciding with an increase in free elastase during exacerbations [8, 22, 23]. Furthermore, higher urinary concentrations of desmosine have been associated with faster decline in FEV1 in COPD [24]. Finally, during exacerbations, it has been observed that there is a decrease in plasma antioxidant capacity [25].

In view of the fact that COPD exacerbations are heterogeneous in terms of both aetiology and inflammation, biomarkers could be useful to phenotype these events. Using unbiased statistical tools, BAFADHEL *et al.* [26] have defined sensitive and specific biomarkers to identify predefined clinical exacerbation phenotypes. Particularly, four biological exacerbation clusters were identified that relate to identifiable patterns of inflammation and potential causative pathogens. Among them, bacterial and eosinophilic clinical exacerbation phenotypes can be identified from the stable state. Following this experience, the same group of authors investigated the usefulness of blood eosinophils to direct corticosteroid therapy during exacerbations [27]. The authors showed that a

biomarker-directed strategy, which used the peripheral blood eosinophil count to guide treatment with corticosteroids, was not associated with an increase in treatment failure or worsening of symptoms compared with standard conventional therapy, while prednisolone prescriptions at exacerbation were safely reduced.

The impact of COPD exacerbations on lung function

A possible link exists between chronic persistent infection/inflammation of the airway and disease progression in COPD patients. This inflammation induces pathological changes, including an increase in sputum production, thickening or oedema of the bronchial wall and bronchoconstriction that may precipitate the limitation of expiratory flow and dynamic hyperinflation [28].

It seems logical that repeated episodes of exacerbations may impair lung tissues and lead to an accelerated rate of decline in pulmonary function in COPD patients. This concept has been evaluated by several experimental observations of the impact of exacerbation frequency on lung decline [1, 29–39]. The oldest studies were less likely to find an effect of exacerbations, in light of several clinical, epidemiological and pathological differences in the understanding of exacerbations. Beside the widely variable criteria used to define frequency and severity of exacerbations, some studies also used questionnaire responses to assess exacerbations, often with a large recall interval that could reduce accuracy.

In 1976, FLETCHER *et al.* [40] reported the results of a 10-year study and found no relationship between lung function decline and chest infections. However, it should be noted that the enrolled patients had mild or no airflow obstruction, the diagnosis of exacerbation was based on a retrospective analysis of the data, and the study possibly lacked the statistical power to identify any effect after adjusting for relevant confounders. In 1979, a study reported an association between a decline in lung function and episodes of lower respiratory tract illnesses, although patients were relatively young with mild airflow obstruction [37]. After that experience, KANNER *et al.* [30] showed that, among smokers, exacerbations are associated with steeper lung function decline. Only active smokers repeatedly showed accelerated loss of lung function, suggesting an interaction between the coexistence of active smoking and the presence of repeated infections. DONALDSON *et al.* [29] showed, for the first time, that patients with moderate-to-severe COPD who suffered frequent exacerbations ($>$2.92 per year) experience a significantly greater decline in FEV1 of 40 mL per year than patients who had infrequent exacerbations ($<$2.92 per year), in whom FEV1 declined by 32 mL per year. Frequent exacerbations were associated with a faster decline in FEV1 if allowance was made for smoking status, although there was only a relatively small effect of smoking, possibly because there was only one smoker in the infrequent exacerbator group. Other major longitudinal studies showed an annual rate of FEV1 decline between 40 and 55 mL, although they have been completed in the context of pharmacological trials, with several limitations [39, 41, 42]. Among those, data from the TORCH (Toward a Revolution in COPD Health) study showed a faster decline in FEV1 among patients experiencing a greater frequency of exacerbations during a 3-year study period [39]. More recently, CASANOVA *et al.* [43] monitored 1198 patients with COPD recruited in Florida, USA, and Tenerife, Spain, from 1997 to 2009. They found that FEV1 declined significantly (by 86 mL per year) in 18% of patients, with higher FEV1 at recruitment and body mass index (BMI) being independent predictors of FEV1 decline.

The frequency of exacerbations varies widely among individuals with similar degrees of COPD severity. Further long-term studies are required to evaluate the effect of exacerbations on disease progression in COPD patients and to ascertain which patient groups are at particular risk of disease progression. It is also necessary to study the effect of exacerbation on disease progression at different stages of the disease.

Systemic consequences of COPD exacerbations

Currently, COPD is defined as a chronic inflammatory disease of the lung with important systemic consequences. During exacerbations, an amplified inflammatory response occurs, both locally and

systemically. It has been postulated that the existence of this increased systemic inflammation during exacerbations may explain some of the extrapulmonary manifestations, especially cardiovascular diseases.

Cardiovascular disorders

COPD patients have frequent comorbid conditions, including coexistent cardiac diseases, that represent risk factors for increased hospital admission, mortality and length of stay [44–48].

COPD patients with an ischaemic heart disease have worse quality of life, more breathlessness and lower exercise capacity. In these patients, exacerbations are not more frequent but the time to symptom recovery is longer than in COPD patients without ischaemic complications [49]. Furthermore, ischaemic heart disease and/or congestive heart failure can increase the rate of treatment failure, thus contributing to the worsening of the patient's condition [45, 46]. Lower respiratory tract infections are one of the main causes of COPD exacerbations that are associated with an acute-phase response, with an increase in systemic inflammatory markers, such as fibrinogen and IL-6. A "spill-over" effect from the lungs to the systemic and cardiac vasculature is conceivable, possibly amplifying the inflammatory processes in atherosclerosis and atherothrombosis. Increased levels of these markers in the blood have been associated with an increased risk of thrombus formation and cardiovascular events.

A recent experience evaluated cardiac-specific troponin T (cTnT) in COPD patients hospitalised because of an exacerbation and found this biomarker to be a strong and independent prognostic factor for mortality after discharge [50]. The same group of researchers found that neutrophils, which are the cells that characterise COPD exacerbations, are positively associated with cTnT elevation in a dose–response manner [51]. The positive association between neutrophils and cTnT elevation is compatible with the concept that an exaggerated inflammatory response in COPD exacerbation predisposes to myocardial injury.

The risk of suffering a heart attack or stroke after presenting with an exacerbation has been studied in a database of 25 857 COPD patients entered in The Health Improvement Network database over a 2-year period [52]. The incidence of myocardial infarction and stroke was 1.1 and 1.4 per 100 patients per year, respectively. Exacerbation of COPD was associated with a 2.27-fold increased relative risk of myocardial infarction during a short, 5-day period, a risk that gradually decreased over time, and an increase of 1.26 in the risk of a stroke 1 to 49 days after the index event.

Diabetes mellitus

Diabetes and acute hyperglycaemia are common in COPD patients. In the general population, females with COPD have a 1.8-fold increased risk of developing type 2 diabetes compared with those without COPD [53]. Furthermore, a previous diagnosis of diabetes can be found in 14–15% of COPD patients hospitalised because of an exacerbation [48, 54]. Increasing blood glucose concentrations are associated with adverse clinical outcomes in patients hospitalised because of an exacerbation of COPD, in terms of both a higher mortality and a longer stay in hospital, in comparison to those with lower blood glucose concentrations [55].

Metabolic syndrome and nutritional abnormalities

Metabolic syndrome is a complex disorder and an emerging clinical challenge, presenting with abdominal obesity, elevated triglycerides, atherogenic dyslipidaemia, elevated blood pressure, high blood glucose levels and/or insulin resistance. The association between the metabolic syndrome and inflammation is well documented: elevation of pro-inflammatory cytokine levels reflects their overproduction by the enlarged adipose tissue mass. In this respect, COPD and metabolic syndrome share common pathophysiological features with chronic systemic inflammation, which has been implicated as a major causative factor for both disorders [56]. A higher frequency of metabolic syndrome can be found among patients with COPD, suggesting a link through the

systemic inflammation shared by both diseases [57–59]. Systemic inflammation may increase the risk of exacerbation in COPD patients with metabolic syndrome. In this context, an association between exacerbation frequency and metabolic syndrome has recently been suggested. In a prospective study, which enrolled 106 COPD patients, it was observed that patients with a metabolic syndrome had a higher frequency (2.4 ± 0.8 *versus* 0.68 ± 0.6) and a longer duration of exacerbations in comparison to the control group [60].

Fat-free mass depletion and loss of skeletal muscle

Among the systemic consequences of COPD, fat-free mass depletion, weight loss and low BMI are independently associated with excess mortality and impairment of quality of life [61, 62]. Almost 40% of hospitalised patients with moderate-to-severe COPD with an exacerbation show nutritional disorders of varying degrees. The number of days of hospitalisation during a COPD exacerbation seems to be related to fat-free mass, muscle mass, BMI, and albumin, while the frequency of hospitalisation is related to a decline in fat-free mass [63, 64]. Loss of skeletal muscle has long been established as a feature of stable COPD [64]. These effects are worse after exacerbations and may be more pronounced due to these patients receiving higher doses of corticosteroids during an acute episode. Interesting data related to the impact of exacerbation on exercise activity have been reported by DONALDSON *et al.* [65]. In a longitudinal study, the investigators quantified the amount of time spent outdoors and found that frequent exacerbators had spent less time outdoors. Furthermore, they identified decreased activity a few days prior to an exacerbation, which remained decreased for up to 5 weeks.

The effect of exacerbations has also been reported using the BODE (body mass, obstruction, dyspnoea and exercise capacity) index, in a study of 205 COPD patients followed prospectively for 2 years with a periodical evaluation of the index [33]. The authors found that exacerbations had a negative impact on the BODE index, particularly in decreasing exercise tolerance, which manifested as a decrease in distance in the 6-min walk test. The BODE index score worsened by 1.38 points during the exacerbation, and remained 0.8 and 1.1 points above baseline at 1 and 2 years, respectively. However, there was little change in BODE index score at 2 years in nonexacerbators.

The impact of COPD exacerbations on daily activity and quality of life

Exacerbations of COPD are associated with substantial symptomatic and physiological deterioration, leading to a dramatic impairment in the feeling of wellbeing, physical activity, mood and social life of COPD patients [66, 67]. The most important aspect of COPD from the patient's perspective is the impact on activities of daily living occurring during exacerbations, as recently demonstrated by MIRAVITLLES *et al.* [68]. The authors showed that this feeling was sustained by the fact that up to 45% of individuals had to stay in bed or on the couch all day during such episodes. These findings have been confirmed by a multinational, cross-sectional, interview-based study evaluating 125 patients with predominantly moderate-to-very severe COPD [69]. Nearly 90% of patients in this study reported that exacerbations had an influence on their activities of daily living, with half of them needing additional help with certain tasks (household chores, shopping and cooking) during an exacerbation. Furthermore, patients with COPD have very low levels of physical activity during and after hospitalisation for an exacerbation, independently of whether the exacerbation is infectious or not [70].

Exacerbations also have a strong influence on mood and cause a variety of negative feelings, such as depression, irritability/bad temper, anxiety, isolation, anger and guilt [31, 69]. COPD patients most commonly cite lack of energy, depression and anxiety when describing their feelings about exacerbations and up to 40% stated that exacerbations affect their relationships with others [69]. The relationship between depressive symptoms, exacerbation frequency, systemic inflammation and social factors has been evaluated in a recent prospective study enrolling 169 stable COPD

patients using the depression scale of the Center for Epidemiologic Studies [71]. The authors found that patients with frequent exacerbations exhibited significantly more depressive symptoms than those with infrequent exacerbations.

Regardless of study design, the criteria used to define the frequency and severity of exacerbation, and instruments to measure the quality of life, exacerbations, especially if they are repeated, worsen health-related quality of life of COPD patients [31, 38, 72–81]. A study by CONNORS *et al.* [82] reported the quality-of-life outcomes in patients hospitalised with exacerbation of COPD. At 6 months, 54% of patients required assistance with at least one activity of daily living and 49% considered their health status to be fair or poor. In the East London cohort study [72], patients with two or fewer exacerbations per year were found to have an average St George Respiratory Questionnaire (SGRQ) total score of 49, whereas patients with three to eight exacerbations per year had an average score of 64. The study by SPENCER *et al.* [38] shown that decline in FEV1 and frequency of exacerbations are two separate factors that lead to deterioration in health status. In a longitudinal study, 613 patients with moderate-to-severe COPD were followed for a maximum of 3 years. The authors found that frequent exacerbations were independently associated with a worse baseline SGRQ score and a more rapid rate of deterioration in health status. Another recent study of 421 patients with COPD revealed a clinically significant deterioration in health status during an exacerbation [75]. This was a reflection of a high score in the SGRQ impact domain ($\geqslant$4-point increase), which persisted in more than half of patients during the first week and one-third of patients during the second week of follow-up. Most of the variables of health status, symptoms and functional state returned to baseline after 14 days with the exception of mental state (39 days).

Not all exacerbations are captured by healthcare contacts; most patients with COPD reported being able to recognise early warning signs of an exacerbation but less than half reported these episodes to healthcare providers. Thus, these patients did not receive professional evaluations and we do not know if they received the correct treatment [69, 72].

Unreported exacerbations have been shown to impact adversely on the patient's health over the intermediate and long term, and therefore cannot be disregarded [73, 83, 84]. In a multicentre prospective cohort of 491 COPD patients, it has been demonstrated that more than one unreported exacerbation was associated with significant worsening of the SGRQ score and quality of life at 1 year [85]. These data underline the importance of improving self-management skills to enhance early detection, and of early and appropriate actions by patients in exacerbation episodes.

The "frequent exacerbator" phenotype

COPD has been increasingly recognised as a markedly heterogeneous disease in which FEV1 seems not to explain fully the variability between individuals. Thus, many studies have attempted to identify and quantify the prevalence of different phenotypes in COPD, using populations of various sources, severities and particularities. The variable frequency of exacerbations has been investigated and understood within this context.

Frequent exacerbations have been associated with increased dyspnoea and reduced exercise capacity, greater decline in health status, and increased likelihood of becoming housebound [29, 68, 76, 86, 87]. It is estimated that patients with COPD have an average of between one and four exacerbations per year with a large inter-individual variability, in such a way that some cases just present decompensation while others suffer repeatedly [88].

Using data from the large observational ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) cohort, HURST *et al.* [89] examined the frequency of exacerbations among patients with moderate, severe or very severe COPD. Using a definition of exacerbation based on healthcare utilisation, they found that a history of previous exacerbations best predicted the subsequent occurrence of exacerbations at all stages of COPD severity. Moreover, although the frequency and severity of exacerbations did increase with disease severity,

patients with frequent exacerbations (defined as two or more per year) and those with infrequent exacerbations (defined as fewer than two exacerbations per year) tended to remain in the same category of exacerbation frequency for all 3 years of the study, irrespective of disease severity. The authors interpreted this stability of exacerbation frequency as evidence that patients who have frequent exacerbations represent a distinct COPD phenotype, implying the existence of some underlying genetic, biological or behavioural mechanism that determines susceptibility or resistance to recurrent exacerbations, independent of disease severity.

A recent evaluation of long-term natural history of COPD in terms of successive severe exacerbations and mortality confirmed these findings. SUISSA *et al.* [90] studied a large population-based inception cohort of COPD patients from 1990 to 2005 with a long-term follow-up, using the healthcare databases from the province of Quebec, Canada. COPD patients were followed to the first severe exacerbation requiring hospital admission and then followed on through successive exacerbations. The authors reported that each successive exacerbation was associated with a decreased inter-exacerbation interval until death. Furthermore, they showed that the occurrence of every new severe exacerbation requiring hospitalisation worsens the course of the disease and increases the risk of a subsequent exacerbation, with patients 25 times more likely to be readmitted after their 10th COPD hospitalisation than after their first COPD hospitalisation. These findings suggest that exacerbations may not recover to the usual stable state, and may be associated with increased airway inflammation, lung function decline, increased bacterial colonisation and, thus, increased susceptibility to further exacerbations. Finally, the authors provided data suggesting that phenotypes observed in stable COPD patients and at exacerbation seem not to be independent phenomena and that recovery from exacerbation alters the susceptibility to future events (fig. 1) [91].

The mechanisms for these observations are not totally clear but may include suboptimal therapy of the exacerbations or secondary bacterial infection leading to up-regulation of airway inflammation and receptors for human viruses. The importance of early presentation and appropriate intervention at COPD exacerbation that shortens exacerbation recovery and chance of hospital admission should be emphasised.

The impact of COPD exacerbations on mortality

COPD *per se* has an important impact on worldwide mortality; a recent report showed that COPD is now the third cause of death in the world, after ischaemic heart disease and stroke [92].

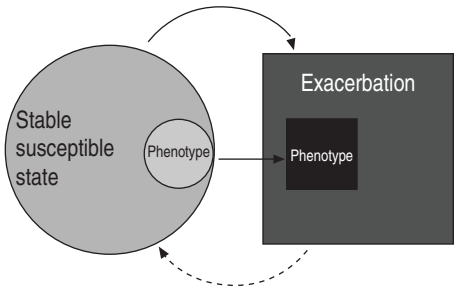

Figure 1. Disease phenotyping and the pathogenesis of chronic obstructive pulmonary disease (COPD) exacerbation. Phenotypes observed in stable COPD and at exacerbation are not independent phenomena (solid arrow): recovery from exacerbation alters the susceptibility to future events (dashed arrow). Reproduced and modified from [91] with permission from the publisher.

Exacerbations that require hospitalisation have an in-hospital mortality rate of 11% and 24% and lead to a mortality rate of 22% and 35.6% after 1 and 2 years, respectively [8, 93, 94]. Traditionally, this increase in mortality has been explained on the basis of greater baseline severity of the disease and none of these studies have specifically examined the prognostic influence of exacerbation by itself. However, recent data suggest that exacerbations may have a direct effect on mortality, independent of the baseline mortality of the disease [95–98].

SOLER-CATALUÑA *et al.* [95] were the first to report that severe exacerbation of COPD has an independent negative prognostic impact. In a cohort of 304 male patients followed for 5 years, the authors observed how the frequency of exacerbations increased the risk of death regardless of other prognostic variables. Among patients who had one or two severe exacerbations treated in hospital, the risk for death was double (95% CI 1.01–3.98) and frequent exacerbators (three or more

exacerbations per year) had a risk of death 4.3 times greater (95% CI 2.62–7.02) than patients requiring no hospital management. The severity of exacerbation was also important, since hospitalised patients showed a higher mortality than those treated as an emergency without being hospitalised. Thus, exacerbation itself may be a significant factor associated with increased mortality in COPD but the severity of the underlying disease may influence the patient's outcome.

These results have been replicated in a second observational study in 185 patients by the same group of authors [96]. The main finding of this second study was that severe exacerbations of COPD imply an increased mortality risk that is independent of baseline severity of the disease as measured by the BODE index [96]. In line with these findings, ESTEBAN *et al.* [97], in a study of 611 patients with COPD followed for 5 years, found that hospitalisation was associated independently with both respiratory mortality and mortality from all causes. In a prospective cohort study, ALFAGEME *et al.* [98] found that a high frequency of exacerbations has an independent negative impact on the prognosis of COPD patients. Finally, in a large population-based cohort of COPD patients with long-term follow-up, SUISSA *et al.* [90] showed that every new severe exacerbation increases the risk of death, by up to five times after their tenth compared with after their first COPD hospitalisation. This mortality peaks in the first week after admission for a COPD hospitalisation and stabilises after 3 months, dropping eight-fold.

Given the importance of these severe exacerbations, it has been proposed that the number of these events will be part of multidimensional prognostic predictive scales. The prognostic capacity of the BODEX index, a multidimensional index similar to BODE in which frequency of exacerbations replace exercise capacity, has been shown to be similar to that of the BODE [95]. Along the same line, a simple four-component index, the DOSE (dyspnoea, airflow obstruction, smoking status and exacerbation frequency) index, has been derived using data from 375 patients with COPD in primary care and validated in cross-sectional and longitudinal samples in various healthcare settings in the Netherlands, Japan and the UK [99]. The DOSE index provides clinicians with a wider perspective on COPD severity than is encompassed by any of its component items. The four components also provide a guide to disease management.

During recent years, it has been shown that increasing exacerbation frequency is associated with higher mortality, while exacerbations appear to cluster in time, and a history of exacerbations is the single best predictor of future exacerbations. Thus, rather than the smooth, gradual decay of the curve proposed by FLETCHER and PETO [1], these findings evoke a stepwise component to the deterioration in COPD over time, as recently proposed by HANSEL and BARNES [100] (fig. 2).

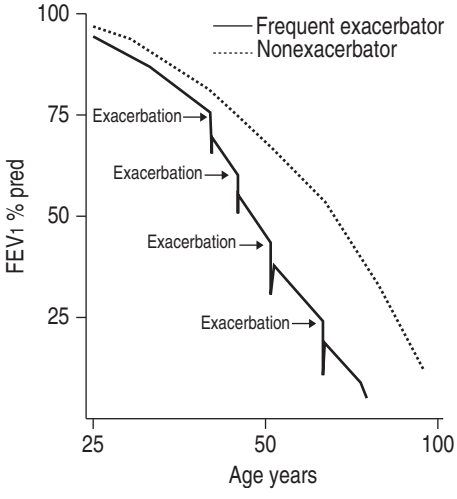

Figure 2. A model of the impact of exacerbations on the natural history of the disease in chronic obstructive pulmonary disease patients. FEV1: forced expiratory volume in 1 s; % pred: % predicted. Reproduced and modified from [100] with permission from the publisher.

Conclusions

COPD is a partially reversible disorder characterised by progressive airflow obstruction, the course of which is punctuated by episodes of acute symptomatic worsening (exacerbations) of variable severity and frequency. Exacerbations represent crucial events in the natural history of COPD patients, and are associated with increased airway inflammatory changes and considerable physiologic deterioration, including acceleration of the decline in lung function and exercise tolerance. During the past decades, there has been much interest in exacerbations as they strongly influence health-related quality of life and activities of daily living of COPD patients, resulting in an increase in hospitalisations and mortality, and for all of these reasons

contributing significantly to excess healthcare costs. Although exacerbations become more frequent and more severe as COPD progresses, the rate at which they occur appears to reflect an independent susceptibility phenotype. It is clear that the approach to treatment according to this phenotype could represent a significant change in the management of COPD, from treatment focused on the severity of the airflow limitation to a more personalised approach directed by clinical features.

Statement of Interest

None declared.

References

1. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977; 1: 1645–1648.
2. Keatings VM, Barnes PJ, Schellenberg D, *et al.* Granulocyte activation markers in induced sputum: comparison between chronic obstructive pulmonary disease, asthma, and normal subjects vitamin D binding protein variants and the risk of COPD. *Am J Respir Crit Care Med* 1997; 155: 449–453.
3. Bhowmik A, Seemungal TAR, Sapsford RJ, *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000; 55: 114–200.
4. Mercer PF, Shute JK, Bhowmik A, *et al.* MMP-9, TIMP-1 and inflammatory cells in sputum from COPD patients during exacerbation. *Respir Res* 2005; 6: 151.
5. Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
6. Tsoumakidou M, Siafakas NM. Novel insights into the aetiology and pathophysiology of increased airway inflammation during COPD exacerbations. *Respir Res* 2006; 7: 80.
7. Caramori G, Romagnoli M, Casolari P, *et al.* Nuclear localisation of p65 in sputum macrophages but not in sputum neutrophils during COPD exacerbations. *Thorax* 2003; 58: 348–351.
8. Crooks SW, Bayley DL, Hill SL, *et al.* Bronchial inflammation in acute bacterial exacerbations of chronic bronchitis: the role of leukotriene B4. *Eur Respir J* 2000; 15: 274–280.
9. Stanescu D, Sanna A, Veriter C, *et al.* Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; 51: 267–271.
10. Zhu J, Qiu YS, Majumdar S, *et al.* Exacerbations of bronchitis: bronchial eosinophilia and gene expression for interleukin-4, interleukin-5, and eosinophil chemoattractants. *Am J Respir Crit Care Med* 2001; 164: 109–116.
11. Fiorini G, Crespi S, Rinaldi M, *et al.* Serum ECP and MPO are increased during exacerbations of chronic bronchitis with airway obstruction. *Biomed Pharmacother* 2000; 54: 274–278.
12. Schols AM, Buurman WA, Staal van den Brekel AJ, *et al.* Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996; 51: 819–824.
13. Wedzicha JA, Seemungal TA, MacCallum PK, *et al.* Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. *Thromb Haemost* 2000; 84: 210–215.
14. Pinto-Plata VM, Mullerova H, Toso JF, *et al.* C-reactive protein in patients with COPD, control smokers and non-smokers. *Thorax* 2006; 61: 23–28.
15. Piehl-Aulin K, Jones I, Lindvall B, *et al.* Increased serum inflammatory markers in the absence of clinical and skeletal muscle inflammation in patients with chronic obstructive pulmonary disease. *Respiration* 2009; 78: 191–196.
16. Hurst JR, Donaldson GC, Perera WR, *et al.* Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 174: 867–874.
17. Groenewegen KH, Dentener MA, Wouters EF. Longitudinal follow-up of systemic inflammation after acute exacerbations of COPD. *Respir Med* 2007; 101: 2409–2415.
18. Soler N, Esperatti M, Ewing S, *et al.* Sputum purulence-guided antibiotics use in hospitalised patients with exacerbations of COPD. *Eur Respir J* 2012; 40: 1344–1353.
19. Dahl M, Tybjaerg-Hansen A, Vestbo J, *et al.* Elevated plasma fibrinogen associated with reduced pulmonary function and increased risk of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1008–1011.
20. Donaldson GC, Seemungal TAR, Patel IS, *et al.* Airway and systemic inflammation and decline in lung function in patients with COPD. *Chest* 2005; 128: 1995–2004.
21. Eagan TML, Ueland T, Wagner PD, *et al.* Systemic inflammatory markers in COPD: results from the Bergen COPD cohort study. *Eur Respir J* 2010; 35: 540–548.
22. Viglio S, Iadarola P, Lupi A, *et al.* MEKC of desmosine and isodesmosine in urine of chronic destructive lung disease patients. *Eur Respir J* 2000; 15: 1039–1045.

23. Gompertz S, O'Brien C, Bayley DL, *et al.* Changes in bronchial inflammation during acute exacerbations of chronic bronchitis. *Eur Respir J* 2001; 17: 1112–1119.
24. Gottlieb DJ, Stone PJ, Sparrow D, *et al.* Urinary desmosine excretion in smokers with and without rapid decline of lung function: the Normative Aging Study. *Am J Respir Crit Care Med* 1996; 154: 1290–1295.
25. Rahman I, Skwarska E, MacNee W. Attenuation of oxidant/antioxidant imbalance during treatment of exacerbations of chronic obstructive pulmonary disease. *Thorax* 1997; 52: 565–568.
26. Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662–671.
27. Bafadhel M, McKenna S, Terry S, *et al.* Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; 186: 48–55.
28. O'Donnell DE, Parker CM. COPD exacerbations. Pathophysiology. *Thorax* 2006; 61: 354–361.
29. Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–452.
30. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV1 decline in current smokers but not exsmokers with mild chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 358–364.
31. Miravitlles M, Ferrer M, Pont A, *et al.* Effect of exacerbations on quality of life in patients with chronic obstructive pulmonary disease: a 2 year follow up study. *Thorax* 2004; 59: 387–395.
32. Makris D, Moschandreas J, Damianaki A, *et al.* Exacerbations and lung function decline in COPD: new insights in current and ex-smokers. *Respir Med* 2007; 101: 1305–1312.
33. Cote CG, Dordelly LJ, Celli BR. Impact of COPD exacerbations on patient-centered outcomes. *Chest* 2007; 131: 696–704.
34. Wilkinson TMA, Donaldson GC, Johnston SL, *et al.* Respiratory syncytial virus, airway infl ammation, and FEV1 decline in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006; 173: 871–876.
35. Howard P. Along-term follow-up of respiratory symptoms and ventilatory function in a group of working men. *Br J Ind Med* 1970; 27: 326–333.
36. Bates DV. The fate of the chronic bronchitic: a report of the ten-year follow-up in the Canadian Department of Veteran's Affairs coordinated study of chronic bronchitis. The J. Burns Amberson Lecture of the American Thoracic Society. *Am Rev Respir Dis* 1973; 108: 1043–1065.
37. Kanner RE, Renzetti AD Jr, Klauber MR, *et al.* Variables associated with changes in spirometry in patients with obstructive lung diseases. *Am J Med* 1979; 67: 44–50.
38. Spencer S, Calverley PM, Burge PS, *et al.* Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J* 2004; 23: 698–702.
39. Celli BR, Thomas NE, Anderson JA, *et al.* Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 178: 332–338.
40. Fletcher CM, Peto R, Tinker CM, *et al.* The Natural History of Chronic Bronchitis and Emphysema. Oxford, Oxford University Press, 1976.
41. Anthonisen NR, Connett JE, Kiley JP, *et al.* Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1: the Lung Health Study. *JAMA* 1994; 272: 1497–1505.
42. Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
43. Casanova C, de Torres JP, Aguirre-Jaime A, *et al.* The progression of chronic obstructive pulmonary disease is heterogeneous: the experience of the BODE cohort. *Am J Respir Crit Care Med* 2011; 184: 1015–1021.
44. GOLD Executive and Science Committees. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: GOLD Executive Summary updated 2009. www.gold-copd.org Date last updated: February, 2013.
45. Dewan NA, Rafique S, Kanwar B, *et al.* Acute exacerbation of COPD. Factors associated with poor outcome. *Chest* 2000; 117: 662–671.
46. Adams SG, Melo J, Luther M, *et al.* Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest* 2000; 117: 1345–1352.
47. Murata GH, Gorby MS, Kapsner CO, *et al.* A multivariate model for predicting hospital admissions for patients with decompensate chronic obstructive pulmonary disease. *Arch Intern Med* 1992; 152: 82–86.
48. Antonelli Incalzi R, Fuso L, De Rosa M, *et al.* Co-morbidity contributes to predict mortality of patients with chronic obstructive pulmonary disease. *Eur Respir J* 1997; 10: 2794–2800.
49. Patel AR, Donaldson GC, Mackay AJ, *et al.* The impact of ischemic heart disease on symptoms, heath status, and exacerbations in patients with COPD. *Chest* 2012; 141: 851–857.
50. Brekke PH, Olmland T, Holmedadl SH, *et al.* Troponin T elevation and long-term mortality afther chronic obstructive pulmonary disease exacerbation. *Eur Respir J* 2008; 31: 563–570.
51. Brekke PH, Omland T, Holmedal SH, *et al.* Determinants of cardiac troponin T elevation in COPD exacerbation – a cross-sectional study. *BMC Pulm Med* 2009; 9: 35.

52. Donaldson GC, Hurst JR, Smith CJ, *et al.* Increased risk of myocardial infarction and stroke following exacerbation of chronic obstructive pulmonary disease. *Chest* 2010; 137: 1091–1097.
53. Rana JS, Mittleman MA, Sheikh J, *et al.* Chronic obstructive pulmonary disease, asthma and risk of type 2 diabetes in women. *Diabetes Care* 2004; 27: 2478–2484.
54. Loukides S, Polyzogopoulos D. The effect of diabetes mellitus on the outcome of patients with chronic obstructive pulmonary disease exacerbated due to respiratory infections. *Respiration* 1996; 63: 170–173.
55. Baker EH, Janaway CH, Philips BJ, *et al.* Hyperglycaemia is associated with poor outcomes in patient admited to hospital with acute exacerbations of chronic obstructive pulmonary disease. *Thorax* 2006; 61: 284–289.
56. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; 365: 1415–1428.
57. Marquis K, Maltais F, Duguay V, *et al.* The metabolic syndrome in patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil* 2005; 25: 226–232.
58. Watz H, Waschki B, Kirsten A, *et al.* The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. *Chest* 2009; 136: 1039–1046.
59. Lam KB, Jordan RE, Jiang CQ, *et al.* Airflow obstruction and metabolic syndrome: the Guangzhou Biobank Cohort Study. *Eur Respir J* 2010; 35: 317–323.
60. Küpeli E, Ulubay G, Ulasli SS, *et al.* Metabolic syndrome is associated with increased risk of acute exacerbation of COPD: a preliminary study. *Endocrine* 2010; 38: 76–82.
61. Schols AMWJ, Broekhuizen R, Weling Scheepers CA, *et al.* Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2005; 82: 53–59.
62. Mostert R, Goris A, Weling-Scheepers C, *et al.* Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 2000; 94: 859–867.
63. Girón R, Matesanz C, García-Río F, *et al.* Nutritional state during COPD exacerbation: clinical and prognostic implications. *Ann Nutr Metab* 2009; 54: 52–58.
64. Hopkinson NS, Tennant RC, Dayer MJ, *et al.* A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. *Respir Res* 2007; 8: 25.
65. Donaldson GC, Wilkinson TM, Hurst JR, *et al.* Exacerbations and time spent outdoors in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005; 171: 446–452.
66. Garcia-Aymerich J, Lange P, Benet M, *et al.* Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. *Thorax* 2006; 61: 772–778.
67. Haughney J, Partridge MR, Vogelmeier C, *et al.* Exacerbations of COPD: quantifying the patient's perspective using discrete choice modelling. *Eur Respir J* 2005; 26: 623–629.
68. Miravitlles M, Anzueto A, Legnani D, *et al.* Patient's perception of exacerbation of COPD – the PERCEIVE study. *Respir Med* 2007; 101: 453–460.
69. Kessler R, Stähl E, Vogelmeir C, *et al.* Patient undestainding, detection, and experience of COPD exacerbations. An observational, interview-based study. *Chest* 2006; 130: 133–142.
70. Pitta F, Troosters T, Probst VS, *et al.* Physical activity and hospitalization for exacerbations of COPD. *Chest* 2006; 129: 536–544.
71. Quint JK, Baghai-Ravary R, Donaldson GC, *et al.* Relationship between depression and exacerbations in COPD. *Eur Respir J* 2008; 32: 53–60.
72. Seemungal TAR, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 157: 1418–1422.
73. Langsetmo L, Platt RW, Ernst P, *et al.* Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. *Am J Respir Crit Care Med* 2008; 177: 396–401.
74. Soler JJ, Sánchez L, Román P, *et al.* Risk factors of emergency care and admissions in COPD patients with high consumption of health resources. *Respir Med* 2004; 98: 318–329.
75. Bourbeau J, Ford G, Zackon H, *et al.* Impact on patients' health status following early identification of a COPD exacerbation. *Eur Respir J* 2007; 30: 907–913.
76. Spencer S, Jones PW, for the GLOBE Study Group. Time course of recovery of health status following an infective exacerbation of chronic bronchitis. *Thorax* 2003; 58: 589 –593.
77. Wilson R, Schentag JJ, Ball P, *et al.* A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther* 2002; 24: 639–652.
78. Burge PS, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
79. Doll H, Grey-Amante P, Duprat-Lomon I, *et al.* Quality of life in acute exacerbation of chronic bronchitis: results from a German population study. *Respir Med* 2002; 96: 39 –51.
80. Osman IM, Godden DJ, Friend JA, *et al.* Quality of life and hospital re-admission in patients with chronic obstructive pulmonary disease. *Thorax* 1997; 52: 67–71.
81. Fan VS, Curtis JR, Tu SP, *et al.* Using quality of life to predict hospitalization and mortality in patients with obstructive lung diseases. *Chest* 2002; 122: 429–436.
82. Connors AF Jr, Dawson NV, Thomas C, *et al.* Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med* 1996; 154: 959–967.

83. Seemungal TA, Donaldson GC, Bhowmik A, *et al.* Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161: 1608–1613.
84. Vijayasaratha K, Stockley RA. Reported and unreported exacerbations of COPD: analysis by diary cards. *Chest* 2008; 133: 34–41.
85. Xu W, Collet JP, Shapiro S, *et al.* Negative impact of unreported COPD exacerbations on health-related quality of life at 1 year. *Eur Respir J* 2010; 35: 1022–1030.
86. Jenkins CR, Jones PW, Calverley PM, *et al.* Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomized, placebo-controlled TORCH study. *Respir Res* 2009; 10: 59.
87. Spencer S, Calverley PMA, Burge S, *et al.* Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 163: 122–128.
88. Miravitlles M, Guerrero T, Mayordomo C, *et al.* Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. *Respiration* 2000; 67: 495–501.
89. Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.
90. Suissa S, Dell'aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax* 2012; 67: 957–963.
91. Hurst JR. Exacerbation phenotyping in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2011; 184: 625–630.
92. Lozano R, Naghavi M, Foreman K, *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2013; 15: 2095–2128.
93. Almagro P, Calbo E, Ochoa de Echaguen A, *et al.* Mortality after hospitalization for COPD. *Chest* 2002; 121: 1441–1448.
94. Groenewegen KH, Schols AM, Wouters EF. Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. *Chest* 2003; 124: 459–467.
95. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, *et al.* Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* 2005; 60: 925–931.
96. Soler-Cataluña JJ, Martínez-García MA, Sánchez L, *et al.* Severe exacerbations and BODE index: two independent risk factors for death in male COPD patients. *Respir Med* 2009; 103: 692–699.
97. Esteban C, Quintana JM, Aburto M, *et al.* Predictors of mortality in patients with stable COPD. *J Gen Intern Med* 2008; 23: 1829–1834.
98. Alfageme I, Reyes N, Merino M, *et al.* The effect of airfl ow limitation on the cause of death in patients with COPD. *Chron Respir Dis* 2010; 7: 135–145.
99. Jones RC, Donaldson GC, Chavannes NH, *et al.* Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE index. *Am J Respir Crit Care Med* 2009; 180: 1189–1195.
100. Hansel TT, Barnes PJ. New drugs for exacerbations of chronic obstructive pulmonary disease. *Lancet* 2009; 374: 744–755.

Chapter 10

Antibiotic treatment and prevention of exacerbations of COPD

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SUMMARY: Chronic obstructive pulmonary disease (COPD) is frequently complicated by recurrent exacerbations. These are events in the natural course of the disease characterised by a change in the patient's baseline symptoms that is beyond day-to-day variations, is acute in onset and may require a change in regular medication. Exacerbations are mainly caused by respiratory infections of viral and bacterial aetiology. Since they are associated with high morbidity and mortality their treatment and prevention are important goals of the management of COPD. Antibiotics seem to have a beneficial effect especially in exacerbations with purulent sputum. Their use is mainly indicated in severe exacerbations that require hospitalisation, and for patients that have risk factors for poor outcome. The choice of the antibiotic is based upon the medical history, the local patterns of resistance and the severity of the underlying condition.

Approved strategies for the prevention of exacerbations include smoking cessation and rehabilitation programmes, drug therapy and vaccination. Antibiotic prophylaxis has been a field of research. Macrolides and fluoroquinolones are currently being investigated with promising results. Until strong evidence becomes available, their use should be confined to selected patients, mainly in those with purulent expectorants.

KEYWORDS: Antibiotics, azithromycin, bacteria, COPD, exacerbations, moxifloxacin

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Eur Respir Monogr 2013; 60: 96–106.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017812
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Chronic obstructive pulmonary disease (COPD) is a progressive chronic disease characterised by a decline in respiratory function, exercise capacity and health status [1]. The disease is frequently complicated by recurrent exacerbations of symptoms, which vary in severity and frequency both between patients and during the course of the illness. Acute exacerbations of COPD (AECOPD) are considered a major cause of morbidity and mortality while, in developed countries, the economic burden of the disease placed on health resources for the management of

these events is immense [2, 3]. The clinical significance of AECOPD in the natural course of the disease is well underlined in major international guidelines [1, 4]. COPD exacerbations are responsible for the decline of lung function, the limitation of the patient's activity and deterioration in their quality of life. Exacerbations range from mild events to severe deviations of the disease, which can result in the patient being admitted to the intensive care unit (ICU). Nosocomial mortality of COPD exacerbations is estimated at 10% for patients with elevated levels of carbon dioxide while for those who are admitted to the ICU it is about 40% [5].

Definitions and classification

The heterogeneity of COPD is well recognised and so is that of the exacerbations. Although there is much interest concerning these events, there is also still much debate regarding how exacerbations should be defined; the aetiology, management and their prevention. The definition of an exacerbation remains unclear and is generally based upon different combinations of symptoms, such as an increase of cough and sputum production, worsening of dyspnoea or changes in the consistency of sputum and purulence. Until now the most referenced definition remains that given by ANTHONISEN *et al.* [6], according to which patients are divided into three groups based on their symptoms: Type I exacerbations are defined by the presence of increased dyspnoea, sputum volume and sputum purulence; Type II exacerbations are defined by the presence of two of these symptoms; and Type III exacerbations are defined by the presence of one of these symptoms in addition to one of the following: an upper respiratory tract infection in the past 5 days, fever without other cause, increased wheezing or cough, or 20% increase in heart rate or respiratory rate when compared with baseline readings. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines defined an exacerbation of COPD as "an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD" [4].

The severity of an exacerbation is sometimes also defined in terms of increasing healthcare utilisation *i.e.* mild (self-managed by the patient at home), moderate (requiring treatment by a family physician and/or hospital out-patient attendance) or severe (resulting in hospital admission), and/or according to aetiology as infective or non-infective [4]. The severity of the exacerbation and the extent of healthcare utilisation are associated with the severity of the underlying disease and the presence of comorbidities (table 1). For this reason a patient with severe COPD with a minor change of a previously stable disease might appear as a moderate to a severe exacerbation requiring medical treatment, while a patient with mild disease and a significant change might appear as a mild exacerbation, since this patient may not seek medical assistance. This fact stresses the importance for the physician to define not only the severity of the exacerbation but also the severity of the underlying disease and to note the number of annually occurring exacerbations, since it defines the severity of COPD [1]. The frequency of exacerbation increases in relation to the severity of the disease. In patients with severe COPD the annual rate of exacerbations is approximately 3.43 per year, while in patients with moderate COPD the expected number of exacerbations is 2.68 per year [7]. Patients with forced expiratory volume in 1 s (FEV_1) >0% present with 1.6 ($\pm$1.5 SD) exacerbations per year while patients with FEV_1 59–40% and FEV_1 <40% present with 1.9 ($\pm$1.8) and 2.3 ($\pm$1.9) exacerbations per year, respectively [8]. Patients with frequent exacerbations during a period of time will continue to suffer a high exacerbation frequency, suggesting patients' particular characteristics make them prone to develop recurrent episodes.

Table 1. Indications for hospital admission of acute exacerbations of chronic obstructive pulmonary disease (COPD) patients

Deterioration of symptoms
Severe underlying COPD
Onset of new physical signs
Failure of initial treatment
Significant comorbidities
Frequent exacerbations
Newly occurring arrhythmias
Diagnostic uncertainty
Older age
Insufficient home support

Nonetheless, the exact nature of these characteristics has not yet been elucidated, although it has been emphasised that the exacerbation frequency is related to the severity of the underlying disease and the number of previous exacerbations [8]. For this reason many studies used diary cards of symptoms that are completed by the patient (once or twice a week) in an attempt to assess the onset/duration of exacerbations and the day-to-day variability of the symptoms [2, 9].

Comorbidities (especially cardiopulmonary disease) play an important role in the clinical presentation of COPD patients because they increase the risk of hospital admission and mortality, while coronary artery disease and/or congestive heart failure increase the possibility of treatment failure to these patients [10]. Elderly age is considered as an independent risk factor for serious exacerbations leading to hospital admission or even death [11]. The differential diagnosis of AECOPD includes an important number of conditions (table 2).

Pathology

AECOPD represent a further intensification of the inflammatory response of the airways, triggered by bacterial and viral infections or by environmental factors. The involved inflammatory mechanisms are unclear and the majority of the available information is coming from *post mortem* studies, bronchial biopsies and the use of noninvasive surrogate markers. In the bronchial wall and bronchoalveolar lavage fluid (BALF) samples from patients with AECOPD, an increased neutrophil count and elevated inflammatory markers, such as interleukin (IL)-6, CXC chemokine ligand (CXCL)8, endothelin-1, leukotriene (LT)B_4 and neutrophil elastase, have been found [12]. According to the theory, on the one had the inflammatory markers, after the resolution of an exacerbation, do not reach the pre-exacerbation levels leading to a subsequent decline in lung function, while on the other hand, the presence of inflammatory markers in induced sputum is related to the appearance of symptoms at baseline and during exacerbations, presenting a relationship between IL-8 and IL-6 levels and frequency of exacerbations [12]. During an exacerbation the lung hyperinflation and air trapping are increased, expiratory flows are decreased leading to increased dyspnoea and ventilation/perfusion disturbances are deteriorated leading to severe hypoxaemia [13–15].

Aetiology of exacerbations

AECOPD are of infectious and non-infectious origin. They are usually apparent after a respiratory infection, although a multiple of other factors can potentially contribute to this process, such as industrial pollutants, allergens, sedatives and comorbidities that are frequently present in these patients. The cause of AECOPD has been attributed as follows: 25% viral, 25% bacterial, 25% a combination of pathogens (bacterial and viral), and in the remaining 25% the cause is unclear [16]. Healthy individuals are able to maintain a sterile tracheobronchial tree, despite its exposure to microbial inoculum by inhalation or by microaspirations. However, in COPD patients this innate lung defence is impaired as a result of exposure to smoke or other environmental irritants and resulting in two distinct infectious cycles that contribute to a progressive loss in lung function (the vicious-cycle hypothesis) [17].

Table 2. Differential diagnosis of chronic obstructive pulmonary disease exacerbations

Pneumonia
Congestive heart failure
Acute myocardial infraction
Upper respiratory tract infections
Pulmonary embolism
Recurrent aspiration pneumonias
No compliance to the indicated treatment

Bacteria are present in significant concentrations in the airways of healthy adults (4%), in patients with stable COPD (29%), and in patients with COPD exacerbations (54%). The detection of bacteria is well correlated with purulent sputum during an exacerbation, thereby providing evidence of their pathogenic role [18]. The most common microbial pathogens related to COPD exacerbations are listed in table 3. Nontypeable *Haemophilus influenza* (NTHi) is the most common pathogen and its role is well investigated [19].

Table 3. Main infectious causes of acute exacerbations of chronic obstructive pulmonary disease

Bacteria	Viruses	Atypical bacteria	Fungi
Haemophilus influenzae	Rhinovirus	*Chlamydophila pneumoniae*	*Pneumocystis jiroveci*
Streptococcus pneumoniae	Parainfluenza virus	*Mycoplasma pneumoniae*	
Moxarella catarrhalis	Influenza virus		
Pseudomonas aeruginosa	Respiratory syncytial virus		
Enterobacteriaceae	Coronavirus		
Haemophilus haemolyticus	Adenovirus		
Haemophilus parainfluenzae	Human metapneumovirus		
Staphylococcus aureus			

NTHi, *Streptococcus pneumoniae* and *Moxarella catarrhalis* share some common characteristics as they are the causes of two other common respiratory infections: acute otitis media and acute sinusitis, which are related to anatomical abnormalities with impaired drainage of secretions, antecedent viral infections and defects in innate and adaptive immunity. It is possible that acquisition of these pathogens in a patient with COPD and impaired lung defence allows infection development in the lower respiratory tract, with or without clinical manifestations [20]. In the past it was proposed that increased concentrations of bacteria (bacterial load), which chronically colonised the respiratory tract in stable COPD, could account for exacerbations. However, novel studies showed that a change in the bacterial load is an independent risk factor for exacerbation [21]. Bacterial infections of the airways represent a dynamic and complex process while the acquisition of new strains plays an important role in the pathogenesis of exacerbations. *Pseudomonas aeruginosa* and *H. influenzae* are the most common "chronic" bacterial pathogens. *P. aeruginosa* is more frequent in advanced disease, *i.e.* in patients with frequent antibiotic use, patients who are frequently hospitalised, or patients with a history of bronchiectasis [22]. The diagnosis of bacterial infection is difficult. Sputum cultures remain the main diagnostic tool, especially in exacerbations with purulent sputum. However, cultures can be unreliable due to a lack of expectoration, the risk of contamination from the upper respiratory tract, and the presence of different cells in the lower respiratory tract, all of which can be responsible for the false picture of contamination and the fact that 20–30% of patients with stable COPD present with positive sputum cultures without there being any evidence for an infection [23]. Therefore, simply detecting bacteria in sputum samples from patients with COPD does not differentiate colonisation from infection, whereas the use of molecular methods contributes to the discrimination of the newly acquired colonising strains of bacterial pathogens from the pre-existing colonising strains [24]. A recent study examined the importance of bacterial load as a risk factor for exacerbations, using quantitative PCR. According to this study there is a marked increase in bacterial load in colonised patients with AECOPD. The airflow limitation seems to be more severe in patients with a higher bacterial load in the stable state. In addition, it was also observed that a higher bacterial load in the stable state was found to be related to the inhaled corticosteroid dosage [25].

The incidence of atypical bacterial infections in AECOPD is unclear. *Chlamydophila pneumoniae* infections present with an incidence of approximately 3–5% (*Mycoplasma pneumoniae* and *Legionella* spp. are more rare) in studies excluding pneumonias and is defined as an infection when there is strictly a four-fold increase in titre or a positive culture [26–28]. The role of viruses has been formerly recognised and tends to be elucidated with the use of newer diagnostic techniques. Older studies, using cultures or serological methods, report rates of isolation for respiratory viruses that range from 10% to 30% [29, 30]. More recent studies, which have used methods based on PCR, report that viruses are being isolated in 40–60% of exacerbations [31–34]. However, caution must be exercised before concluding that the detection of viral RNA in a sputum sample by means of PCR identifies that virus as a cause of an exacerbation, because viral RNA can be detected in up to 15% of sputum samples during stable COPD and this percentage is even higher

for respiratory syncytial virus (RSV) [31, 35]. This obstacle could be avoided by using quantification viral RNA by PCR and analysing samples collected sequentially during exacerbations and stable periods. Recent studies have demonstrated that co-infection with viruses and bacteria account for approximately 25% of exacerbations, and these episodes tend to be of a greater clinical and physiological severity [18, 36].

Management of exacerbations

The management of AECOPD depends on the severity (risk stratification to choose the appropriate antibiotic) and the cause of infection (bacterial or viral). The proposed criteria by ANTHONISEN *et al.* [6] (often referred to as the Anthonisen criteria) seems to be the most useful in estimating the probability of success with antibiotics, since their use seems to be beneficial in type I and type II exacerbations of bacterial origin (fig. 1) [38, 39]. The goal of the treatment is to minimise the impact of current events (recovery to baseline clinical status, prevention of complications, *e.g.* ICU admission) and to prevent the development of subsequent exacerbations. Clinical resolution of symptoms to baseline represents the optimal outcome, which is related to the eradication of the causative infectious pathogen [10, 40–44].

The prevalence of resistance to penicillin and other drugs among pneumococci usually complicate the empirical treatment of AECOPD. The mechanism of resistance is based on alterations of penicillin-binding proteins, while the majority of resistant isolates are resistant to multiple classes of antimicrobials [37]. The prevalence of penicillin-resistant and multidrug-resistant *S. pneumoniae* varies between regions, thus it is important for the physician to be aware of the local patterns of resistance. Macrolide resistance in *S. pneumoniae* occurs by two mechanisms: either by target-site modification or by efflux of the drug out of the cell. Factors that are associated with macrolide resistance include: the use of macrolides within the last 3 months; the recent use of penicillin or trimethoprim-sulfamethoxazole; age (elderly); and HIV infection [45]. Resistance to fluoroquinolones occurs through mutations of the parC or gyrA genes leading to decreased fluoroquinolone susceptibility, which remains rare in Europe (<1%) [37]. Resistance to tetracyclines has reached high levels in many countries and is not considered an option if pneumococcal infection is suspected.

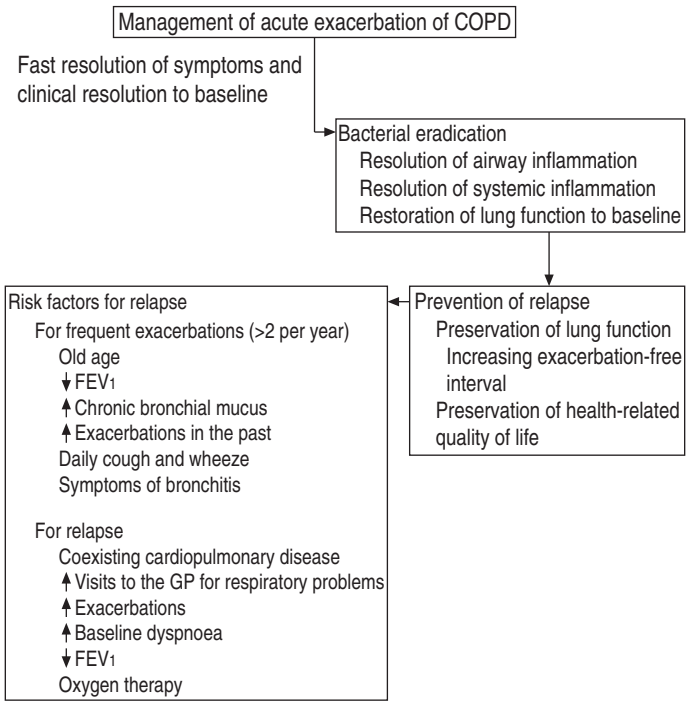

Figure 1. Management of chronic obstructive pulmonary disease (COPD) exacerbations and risk factors for relapse after ambulatory treatment. FEV1: forced expiratory volume in 1 s; GP: general practitioner. Data from [1], [10], [20] and [37].

H. influenzae resistance to β-lactams (β-lactamase production) presents a prevalence of 7.6% [46]. This type of resistance can be overcome with the use of β-lactamase stable cephalosporins or β-lactams plus β-lactamase inhibitors combinations. Efflux pumps are considered to be the main mechanisms that led to macrolide resistance by *H. influenzae* (>98%), while the most potent agent from this class of antibiotics is azithromycin. *H. influenzae* resistance to

fluoroquinolones is rare and the available information concerning tetracycline resistance is limited. Almost all *M. catarrhalis* strains are resistant to penicillin, amoxicillin, ampicillin and piperacillin, while other enzyme-stable β-lactams, macrolides and tetracyclines are very active against this microorganism [37].

The selection of antibiotics in AECOPD exacerbations is based on the causative bacterial pathogen, the severity of the underlying disease, the presence of comorbidities (especially cardiac disease), the presence of risk factors of relapse, and the pattern of antibiotic resistance. Recent antibiotic use (within the last 3 months), as well as recent hospitalisation, places the patient in a high-risk group for harbouring antibiotic resistant pathogens [47–49]. Both the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1] and the European Respiratory Society (ERS)/European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for managing lower respiratory tract infections (fig. 2) [37], suggest that antibiotics should be administered according to the Anthonisen criteria for AECOPD patients with: 1) increased dyspnoea, sputum volume and sputum purulence; 2) with two of the symptoms, if increased purulence of sputum is the one; 3) if they require mechanical ventilation; or 4) if they have severe COPD. The recommended duration of antibiotic therapy is 3–7 days. Mild exacerbations (only one of the three cardinal symptoms) are managed with symptomatic treatment and antibiotics are not prescribed unless the patient's symptoms worsen. Although the evidence of antibiotic use in non-severe exacerbations is weak, a recent study demonstrated the superiority of antibiotic treatment (amoxicillin/clavulanate) for short- and long-term clinical outcomes in moderate exacerbations in patients with mild-to-moderate COPD, when compared with placebo [50]. The optimal antibiotic regimen for the management of COPD exacerbations is still under debate and the selection of an antibiotic is associated to a risk stratification approach. A broader antibiotic regimen should be prescribed for patients at risk of a poor outcome, while *H. influenzae, S. pneumoniae,* and *M. catarrhalis* must be covered empirically, taking into consideration the local pattern of resistance. *P. aeruginosa* and *Enterobacteriaceae* are common in patients with severe COPD.

The first-line antibiotics used include doxycycline, trimethoprim-sulfamethoxazole and amoxicillin. However, amoxicillin is no longer considered a first-line agent because it is inactive against most NTHi and *M. catarrhalis*. In case of hypersensitivity, a tetracycline or a macrolide is a good alternative in countries with low pneumococcal macrolide resistance [50]. Second-line antibiotics include amoxicillin/clavulanate, azithromycin, cephalosporins second or third generation (cefpodoxime, cefprozil or cefuroxime), loracarbef and fluoroquinolones. Outpatients with AECOPD present the same efficacy with doxycycline and trimethoprim-sulfamethoxazole. According to the GOLD guidelines, second-line antibiotics are preferred for patients at risk of a poor outcome (age >65 years, FEV_1 <50%, ⩾3 exacerbations per year, cardiac disease) or if the presence of a resistant microorganism is suspected.

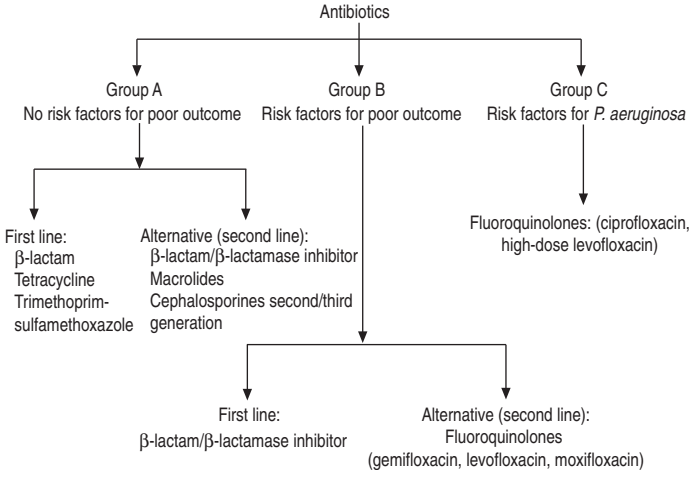

Figure 2. Antibiotic treatment of outpatient management of chronic obstructive pulmonary disease according to both the Global Initiative for Chronic Obstructive Lung Disease and the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guidelines. *P. aeruginosa*: *Pseudonomas aeruginosa*. Data from [1] and [37].

The efficacy of first- and second-line antibiotics has been evaluated in a meta-analysis study, which included 12 randomised trials, where the second-line antibiotic was found to have had had a significantly higher success in treatment (resolution or

improvement of symptoms) without a difference to mortality, adverse events or microbiological outcomes [51]. The efficacy of different second-line antibiotics was compared in another meta-analysis study (macrolides *versus* fluoroquinolones *versus* amoxicillin/clavulanate) and showed no difference in the short-term treatment success (resolution or improvement of symptoms) [52]. However, the use of fluoroquinolones was associated with a higher rate of microbiological success and a lower recurrence rate. Amoxicillin/clavulanate was associated with more adverse effects (diarrhoea).

GLOBE (Gemifloxacin Long term Outcomes in Bronchitis Exacerbations) and MOSAIC (Montelukast Study of Asthma in Children) studies compared the use of newer fluoroquinolones with more traditional antibiotic regimens. Regarding the efficacy, inequivalence has been observed between the comparators. Fluoroquinolones were more potent regarding bacterial eradication, while being associated with a prolonged free-exacerbation interval and fewer relapses [53, 54]. The MAESTRAL study (Moxifloxacin in Acute Exacerbations of Chronic Bronchitis Trial) compared the use of moxifloxacin *versus* amoxicillin/clavulanate in outpatient acute exacerbations of COPD, demonstrating the noninferiority of moxifloxacin to amoxicillin/clavulanate in the treatment of AECOPD [55]. However, in patients with positive cultures at baseline, moxifloxacin proved to be superior to amoxicillin/clavulanate. in terms of clinical failure rates at the 8-week time-point (treatment difference of approximately 6% in favour of moxifloxacin) and bacterial eradication rates, suggesting that this treatment could be preferred for patients with bacteriologically confirmed exacerbation [55].

The risk factors for *Pseudomonas* spp. infection include: recent hospitalisation ($\geqslant$2-day duration during the past 3 months); frequent administration of antibiotics ($\geqslant$4 courses within the past year); severe COPD (FEV_1 <30% of predicted); isolation of *P. aeruginosa* during a previous exacerbation; colonisation during a stable period; and systemic corticosteroid use (>10 mg prednisolone daily in the last 2 weeks) [1, 37, 56]. In these patients influenza vaccination presents a protective factor [57]. The treatment of patients with risk factors for *Pseudomonas* spp. infection includes the administration of fluoroquinolones (ciprofloxacin or a high dose of levofloxacin) (fig. 3).

All patients must be frequently re-evaluated. In case of clinical status worsening or inadequate response within 72 h in their sputum cultures, modification of antibiotics treatment against resistant strains and non-infectious aetiologies of COPD exacerbations must be considered. The choice of the oral or the intravenous route must be based on the patient's condition and the severity of the exacerbation. Change to oral route must be done as soon as possible (from day 3 of admission if the patient's condition is stable). The duration of antibiotic therapy in patients with COPD exacerbation is usually 3–7 days, depending on the patient's response to the treatment. A meta-analysis that compared 5 to $\geqslant$7 days of antimicrobial therapy found no differences in the outcome between the two groups, whereas short- compared to long-term treatment was associated with fewer adverse events [58]. Given the important role of viruses, particularly rhinovirus and influenza virus, in COPD exacerbations, the early use of antiviral agents, especially neuraminidase inhibitors could contribute to the shorter duration of the disease and to the prevention of the complications. However, the effectiveness of those regimens has yet to be proven [59].

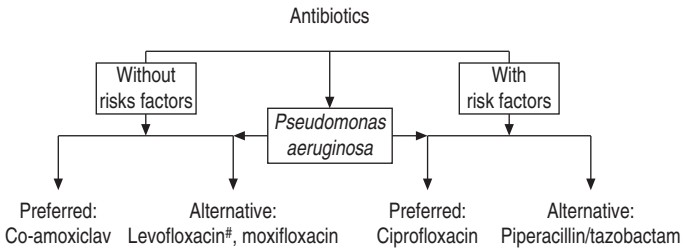

Figure 3. Antibiotic treatment of chronic obstructive pulmonary disease exacerbations in hospitalised patients in accordance with the Global Initiative for Chronic Obstructive Lung Disease guidelines and the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases guidelines. #: 750 mg per day or 500 mg twice daily is an alternative. Data from [37].

Prevention of AECOPD

The prevention of AECOPD is based on non-pharmacological interventions including smoking

cessation, oxygen therapy, noninvasive ventilation and rehabilitation and pharmacological interventions including the adequate use of bronchodilators, corticosteroids, mucolytics, antioxidants, vaccines and possibly the prophylactic use of antibiotics in selected patients. Smoking cessation programmes should be included in the management of these patients because smoking cessation is the only therapy that clearly improves lung loss and survival among patients with mild-to-moderate COPD [60]. Smoking cessation is associated with a reduced risk of COPD exacerbations [61]. The role of pulmonary rehabilitation has been evaluated through a number of clinical trials, but the prevention of exacerbations is unclear. Pulmonary rehabilitation programmes are highly effective and safe in reducing hospital admissions and mortality and improving health-related quality of life (HRQoL) in COPD patients following an exacerbation [62]. The minimum length of an effective rehabilitation programme is 6 weeks; the longer the duration the more effective the results.

The influenza virus has the ability to further damage airway epithelial cells leading to secondary bacterial proliferation. The prevalence of influenza infection in AECOPD is significant, leading to frequent hospitalisations. All patients with COPD should receive influenza vaccination annually [63]. The utility of this intervention is well established because it reduces the number of exacerbations per patient and is associated with fewer outpatient visits, fewer hospitalisations and reduced mortality [64, 65]. Vaccination against *Pneumonococci* should also be considered in patients with COPD, but the value of this intervention is not well established. Recent data found no significant difference on morbidity and mortality [66]. Pneumococcal vaccination is recommended in the elderly (>65 years) and in high risk patients (cardiac disease, chronic pulmonary disease, renal failure, diabetes, cerebrovascular disease, functional or anatomical asplenia, liver disease). Vaccination should be performed with the 23-valent polysaccharide or with the 13-valent conjugate pneumococcal vaccine [44]. Pneumococcal vaccination has no benefit on the hospitalisation of AECOPD but indicates high protection against community-acquired pneumonia (CAP) due to *S. pneumoniae* or unknown aetiology in persons younger than 65 years with an FEV_1 <40% [67].

The interest concerning the prophylactic use of antibiotics is not recent. A number of trials (before 1970) reported a reduction of days of disability without a significant reduction in the number of exacerbations [68–70]. These trials did not support the use of prophylactic antibiotic treatment in COPD patients, while major discrepancies concerning benefits, side-effects and antibiotic resistance development were apparent [71].

Today, the prophylactic use of antibiotics is becoming more popular because of the hypothesis that patients with chronic bacterial colonisation suffer more frequent exacerbations and, therefore, bacterial eradication could lead to a prolonged period of time before the next exacerbation. The interest concerns two main groups of antibiotics: macrolides and fluoroquinolones.

The use of macrolides for the prevention of AECOPD is based on their immunomodulatory and anti-inflammatory effects, which have been recognised in patients with cystic fibrosis and diffuse panbronchiolitis. The immunomodulatory effects of macrolides include reduced sputum and antimicrobial peptide production, inhibition of biofilm formation and reduced production of different virulent factors, while recently antiviral effects have been reported [72]. Many studies have examined the long-term macrolide use for the prevention of AECOPD and seem to provide adequate evidence concerning the prophylactic use of macrolides in COPD exacerbations in selected patients. Adverse events (mainly from the gastrointestinal tract or hearing decrements) have been reported [73–76]. The administration of azithromycin at a dose of 250 $mg \cdot day^{-1}$ for 1 year, in addition to the usual medication, led to a reduction in the frequency of exacerbations, an improvement of patients' quality of life and a decrease of colonisation with selected respiratory pathogens [76]. However, an increased incidence of macrolide-resistant organisms has been observed. The major questions regarding the prophylactic use of macrolides in COPD concern the optimal dose, the type of patient (selected or not), the optimal duration and the impact from the emergence of macrolide-resistant pathogens.

The PULSE (PULSEd moxifloxacin for the prevention of exacerbations of COPD) study, which is a double-blind, placebo controlled trial, has been conducted in stable COPD patients. The study population was randomised to moxifloxacin (400 mg oral daily dose) or placebo for 5 days and this treatment was repeated every 8 weeks for a total of six courses. The intermittent prophylactic pulsed treatment with moxifloxacin led to reduction of AECOPD (19% in the intent-to-treat population and 25% in per protocol end of treatment population) [77]. The pulsed use of moxifloxacin did not have a significant effect in health status, rate of hospitalisation, mortality or decline in lung function in the COPD patients, concluding that it could be used in selected patients, mainly those who report purulent expectoration.

Statement of Interest

None declared.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of Chronic Obstruction Pulmonary Disease 2010. Available from: www.goldcopd.org/
2. Seemungal TAR, Donaldson GC, Paul EA, *et al.* Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 151: 1418–1422.
3. British Thoracic Society. Burden of Lung Disease Report. 2nd Edn. A Statistics Report from the British Thoracic Society 2006. Available from: www.brit-thoracic.org.uk/Portals/0/Library/BTS%20Publications/burdeon_of_lung_disease2007.pdf Date last accessed: March 3, 2013.
4. Celli BR, MacNee W, Agusti A, *et al.* Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
5. Steinmetz J, Rasmussen LS, Nielsen SL. Long-term prognosis for patients with COPD treated in the prehospital setting: is it influenced by hospital admission? *Chest* 2006; 130: 676–680.
6. Anthonisen R, Manfreda J, Warren P, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
7. Donaldson GC, Seemungal TAR, Bhowmik A, *et al.* Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002; 57: 847–852.
8. Miravitlles M, Guerrero T, Mayodomo C, *et al.* Factors associated with increased risk of exacerbation and hospital admission in a cohort of ambulatory COPD patients: a multiple logistic regression analysis. The EOLO Study group. *Respiration (Herrlisheim)* 2000; 67: 495–501.
9. Sapey E, Stockley RA. COPD exacerbations. 2: aetiology. *Thorax* 2006; 61: 250–258.
10. Dewan NA, Rafique S, Kanwar B, *et al.* Acute exacerbation of COPD: factors associated with poor treatment outcome. *Chest* 2000; 117: 662–671.
11. Cydulka RK, McFadden ER Jr, Emerman CL, *et al.* Patterns of hospitalization in elderly patients with asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997; 156: 1807–1812.
12. Bhowmik A, Seemungal TAR, Sapsford RJ, *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000; 55: 114–120.
13. Wedzicha JA. Exacerbations: etiology and pathophysiologic mechanisms. *Chest* 2002; 121: Suppl. 5, 136S–141S.
14. MacNee W. Acute exacerbations of COPD. *Swiss Med Wkly* 2003; 133: 247–257.
15. O'Donnell DE, Parker CM. COPD exacerbations. 3: pathophysiology. *Thorax* 2006; 61: 354–361.
16. Papi A, Bellettato CM, Braccioni F, *et al.* Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; 173: 1114–1121.
17. Sethi S. Infection as a comorbidity of COPD. *Eur Respir J* 2010; 35: 1209–1215.
18. Soler N, Augusti C, Angrill J, *et al.* Bronchoscopic validation of the significance of sputum purulence in severe exacerbations of chronic obstructive pulmonary disease. *Thorax* 2007; 622: 29–35.
19. EldiKa N, Sethi S. Role of non-typeable *Haemophilus influenzae* in exacerbations and progression of COPD. *Curr Opin Pulm Med* 2006; 12: 118–124.
20. Siddiqi A, Sethi S. Optimizing antibiotic selection in treating COPD exacerbations. *Int J Chron Obstruct Pulmon Dis* 2008; 3: 31–44.
21. Sethi S, Sethi R, Eschberger K, *et al.* Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176: 356–561.
22. Eller J, Ede A, Schaberg T, *et al.* Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. *Chest* 1998; 113: 1542–1548.
23. Sykes A, Mallia P, Johnston SL. Diagnosis of pathogens in exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007; 4: 642–646.
24. Sethi S. Molecular diagnosis of respiratory tract infection in acute exacerbations of chronic obstructive pulmonary disease. *Clin Infect Dis* 2011; 52: 290–295.

25. Garcha DS, Thurston SJ, Patel AR, *et al.* Changes in prevalence and load of airway bacteria using quantitative PCR in stable and exacerbated COPD. *Thorax* 2012; 67: 1075–1080.
26. Beaty CD, Grayston JT, Wang SP, *et al. Chlamydia Pneumoniae*, strain TWAR, infection in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991; 144: 1408–1410.
27. Blasi F, Lagnani D, Lombardo VM, *et al. Chlamydia pneumoniae* infection in acute exacerbations of COPD. *Eur Respir J* 1993; 6: 19–22.
28. Smith CB, Golden CA, Kanner RE, *et al.* Association of viral and *Mycoplasma pneumoniae* infections with acute respiratory illness in patients with chronic obstructive pulmonary diseases. *Am Rev Respir Dis* 1980; 121: 225–232.
29. Smith CB, Kanner RE, Golden CA, *et al.* Effect of viral infection on pulmonary function in patients with chronic obstructive pulmonary disease. *J Infect Dis* 1980; 141: 271–280.
30. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 117: Suppl. 2, S286–S291.
31. Seemungal T, Harper-Owen R, Bhowmik A, *et al.* Respiratory viruses, symptoms and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 1618–1623.
32. Rhode G, Wiethege A, Borg I, *et al.* Respiratory viruses in exacerbations of chronic obstructive pulmonary disease requiring hospitalisation: a case-control study. *Thorax* 2003; 58: 37–42.
33. Ko FW, Ip M, Chan PK, *et al.* Viral etiology of acute exacerbations of COPD in Hong-Kong. *Chest* 2007; 132: 900–908.
34. Dimopoulos G, Lerikou M, Tsiodras S, *et al.* Viral epidemiology of acute exacerbations of chronic obstructive pulmonary disease. *Pulm Pharmacol Ther* 2012; 25: 12–18.
35. Ramaswamy M, Groskreutz DJ, Look DC. Recognizing the importance of respiratory syncytial virus in COPD. *COPD* 2009; 6: 64–75.
36. Wilkinson TM, Hurst JR, Perera WR, *et al.* Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD. *Chest* 2006; 129: 317–324.
37. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory infection – full version. *Clin Microbiol Infect* 2011; 17: E1–E59.
38. Nouira S, Marghli S, Belghith M, *et al.* Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo-controlled trial. *Lancet* 2001; 358: 2020–2025.
39. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, *et al.* Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 2: CD004403.
40. White AJ, Gompertz S, Bayley D, *et al.* Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58: 680–685.
41. Adams SG, Melo J, Luther M, *et al.* Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. *Chest* 2000; 117: 1345–1352.
42. MacFarlane JT, Colville A, Guion A, *et al.* Prospective study of aetiology and outcome of adult lower respiratory tract infections in the community. *Lancet* 1993; 341: 511–514.
43. Miravitlles M. Epidemiology of chronic obstructive pulmonary disease exacerbations. *Clin Pulm Med* 2002; 9: 191–197.
44. Sethi S. Acute exacerbations of COPD: A ''multipronged'' approach. *J Respir Dis* 2002; 23: 217–255.
45. Doem GV. Macrolide and ketolide resistance with *Streptococcus pneumoniae. Med Clin North Am* 2006; 90: 1109–1124.
46. Jansen WT, Verel A, Beitsma M, *et al.* Longitudinal European surveillance study of antibiotic resistance of *Haemophilus influenzae. J Antimicrob Chemother* 2006; 58: 873–887.
47. Vanderkooi OG, Low DE, Green K, *et al.* Predicting antimicrobial resistance in invasive pneumococcal infections. *Clin Infect Dis* 2005; 3: 1288–1297.
48. Sethi S, Murphy TF, Cai X, *et al.* Antibiotic exposure in COPD and the development of penicillin and erythromycin resistance in *Streptococcus pneumonia.* ICAAC, San Francisco, 2006; C2-0438.
49. Blasi F, Stolz D, Piffer F. Biomarkers in lower respiratory tract infections. *Pulm Pharmacol Ther* 2010; 23: 501–507.
50. Llor C, Moragas A, Hernández S, *et al.* Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2012; 186: 716–723.
51. Dimopoulos G, Siempos II, Korbila IP, *et al.* Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a meta-analysis of randomized controlled trials. *Chest* 2007; 132: 447–455.
52. Siempos II, Dimopoulos G, Korbila IP, *et al.* Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. *Eur Respir J* 2007; 29: 1127–1137.
53. Wilson R, Schentag JJ, Ball P, *et al.* A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. *Clin Ther* 2002; 24: 639–652.
54. Wilson R, Allegra L, Huchon G, *et al.* Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. *Chest* 2004; 125: 953–964.
55. Wilson R, Anzueto A, Miravitlles M, *et al.* Moxifloxacin *versus* amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. *Eur Respir J* 2012; 40: 17–27.
56. Garcia-Vidal C, Almagro P, Romani V, *et al. Pseudomonas aeruginosa* in patients hospitalised for COPD exacerbations: a prospective study. *Eur Respir J* 2009; 34: 1072–1078.

57. Monsó E, Garcia Aymerich J, Soler N, *et al.* Bacterial infection in exacerbated COPD with changes in sputum characteristics. *Epidemiol Infect* 2003; 131: 799–804.
58. Falagas M, Avgeri S, Matthaiou D, *et al.* Short- *versus* long-term duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. *J Antimicrob Chemother* 2008; 62: 442–450.
59. Wesseling G. Occasional review: influenza in COPD: pathogenesis, prevention and treatment. *Int J Chron Obstruct Pulmon Dis* 2007; 2: 5–10.
60. Anthonisen NR, Skeans MA, Wise RA, *et al.* The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* 2005; 142: 233–239.
61. Au DH, Bryson CL, Chien JW, *et al.* The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. *J Gen Intern Med* 2009; 24: 457–463.
62. COPD Working Group. Pulmonary rehabilitation for patients with chronic pulmonary disease (COPD): an evidence based analysis. *Ont Health Technol Assess Ser* 2012; 12: 1–75.
63. Fiore AE, Shay DK, Broder K, *et al.* Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR Recomm Rep* 2009; 58: 1–52.
64. Gorse GJ, O'Connor TZ, Young SL, *et al.* Impact of a winter respiratory virus season on patients with COPD and association with influenza vaccination. *Chest* 2006; 130: 1109–1116.
65. Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization and mortality in elderly patients with chronic lung disease. *Ann Intern Med* 1999; 130: 397–403.
66. Granger R, Walters J, Poole PJ, *et al.* Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 4: CD001390.
67. Alfageme I, Vasquez R, Reyes N, *et al.* Clinical efficacy of anti-pneumoccocal vaccination in patients with COPD. *Thorax* 2006; 61: 189–195.
68. Johnston RN, McNeill RS, Smith DH, *et al.* Five year winter chemoprophylaxis for chronic bronchitis. *Br Med J* 1969; 4: 265–269.
69. Pridie RB, Datta N, Massey DG, *et al.* A trial of continuous winter chemotherapy in chronic bronchitis. *Lancet* 1960; 2: 723–727.
70. Value of chemoprophylaxis and chemotherapy in early chronic bronchitis. A report to the Medical Research Council by their working party on trials of chemotherapy in early chronic bronchitis. *Br Med J* 1966; 1: 1317–1322.
71. Staykova T, Black PN, Chacko EE, *et al.* Prophylactic antibiotic therapy for chronic bronchitis. *Cochrane Database Syst Rev* 2003; 1: CD004105.
72. Yamaya M, Azuma A, Takizawa H, *et al.* Macrolide effects on the prevention of COPD exacerbations. *Eur Respir J* 2012; 40: 485–494.
73. Suzuki T, Yanai M, Yamaya M, *et al.* Erythromycin and common cold in COPD. *Chest* 2001; 120: 730–733.
74. Banerjee D, Khair OA, Honeybourne D. The effect of oral clarithromycin on health status and sputum bacteriology in stable COPD. *Respir Med* 2005; 99: 208–215.
75. Seemungal TA, Wilkinson TM, Hurst JR, *et al.* Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; 178: 1139–1147.
76. Albert RK, Connett J, Bailey WC, *et al.* Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; 365: 689–698.
77. Sethi S, Jones PW, Theron MS, *et al.* Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Res* 2010; 11: 10.

Chapter 11

Definition and aetiology of non-CF bronchiectasis

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SUMMARY: Bronchiectasis causes significant morbidity and mortality and is characterised by chronic airway inflammation and irreversible dilatation of bronchi. Pathogenesis varies depending on which of the aetiologies is responsible for the disease, and the clinical picture is heterogeneous for the same reason. In addition to conditions in which it is the primary diagnosis, bronchiectasis is associated with a number of diverse conditions such as rheumatoid arthritis and inflammatory bowel disease. Idiopathic bronchiectasis is the most common diagnosis, which emphasises our lack of knowledge about aetiology in many cases. The pattern of bronchiectasis in idiopathic cases tends to be bilateral, cylindrical and lower lobe predominant. Approximately one-third of cases occur post-infection. Severe infection of any sort can damage the bronchial wall sufficiently to cause bronchiectasis localised to the site of infection. Allergic bronchopulmonary aspergillosis, common variable immunodeficiency and primary ciliary dyskinesia are the next most common aetiologies. Non-tuberculous mycobacteria, particularly *Mycobacterium avium* complex, and aspiration are being increasingly recognised as causing bronchiectasis. Bronchiectasis may be present in obstructive airway diseases and, if chronic infection occurs, especially with *Pseudomonas aeruginosa*, it has a profound effect on the clinical course. Aetiology of bronchiectasis should be investigated because it may influence management.

KEYWORDS: Aetiology, allergic bronchopulmonary aspergillosis, bacteria, bronchiectasis, immunodeficiency, primary ciliary dyskinesia

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Eur Respir Monogr 2013; 60: 107–119.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10017912
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

Bronchiectasis is a chronic condition characterised by irreversible dilatation of bronchi. The term irreversible is included because in some conditions, such as pneumonia, dilatation of the airways can be transient (table 1). The airway dilatation is usually caused by damage to the structure of the bronchial wall by the inflammatory processes. The pathogenesis varies depending on the cause of the disease, and the clinical picture is heterogenous for the same reason. The true prevalence of bronchiectasis is unknown. A retrospective study using healthcare organisation data in the USA estimated that 4.2 per 100 000 adults aged 18–34 years had bronchiectasis,

Table 1. Reversibility of high-resolution computed tomography signs of bronchiectasis

Bronchial dilatation	-/(+)
Lobar or segmental volume loss	+
Bronchial wall thickening	++
Mucus plugging of large airways	++
Tree-in-bud pattern	+++

+ to +++: little reversibility to highly reversible; -: irreversible.

increasing to 271.8 per 100 000 in those aged over 75 years [1]. Other studies from Finland and New Zealand have quoted similar prevalence, although attention has been drawn to wide variation influenced by ethnicity; for example, bronchiectasis is more common in children of Pacific Island descent [2, 3].

It is likely that these figures are a significant underestimate of the true prevalence. In addition to cases in which it is the primary diagnosis, bronchiectasis is associated with conditions as diverse as rheumatoid arthritis, inflammatory bowel disease, immune deficiencies and α_1-antitrypsin deficiency, as well as some common conditions such as asthma and chronic obstructive pulmonary disease (COPD). Widespread availability of computed tomography has led to increased recognition of bronchiectasis, particularly milder forms of the disease. However, differentiation must be made between a radiological diagnosis of bronchiectasis, and patients who also have the clinical syndrome. Many patients with interstitial lung disease will have traction bronchiectasis, the phenomenon of distraction of the airways by surrounding retractile fibrosis, without having any susceptibility to airway infections as a consequence. Whereas in other conditions, the presence of bronchiectasis may define a subgroup of patients with regular sputum production, who are prone to airway infections that have a profound effect on the patient's condition and influence management decisions. Studies have suggested that 29–50% of the 1 million COPD patients in the UK have bronchiectasis according to high-resolution computed tomography (HRCT) criteria, and in some cases with severe airflow obstruction this may make them susceptible to chronic infection by the difficult Gram-negative bacterium *Pseudomonas aeruginosa* [4–6].

Bronchiectasis is a condition which involves active chronic inflammation, and patients are prone to frequent exacerbations. In addition to modifying other associated disease processes, it has *per se* significant morbidity, healthcare resource utilisation and mortality. Estimates suggest that healthcare costs per patient are greater than other chronic diseases including heart failure and COPD [1]. Disease activity is driven by a vicious circle of infection, inflammation and tissue damage which further impairs host defences and, in some cases, this leads to disease progression, both in terms of severity of airway damage, and spread of disease into previously undamaged bystander lung. However, the evidence base to direct management of patients with bronchiectasis is lacking and further research is imperative. In two large studies, 26% [7] and 53% [8] of patients, respectively, had no identifiable cause. In this chapter we will describe those aetiologies that have been identified. It is important to investigate the aetiology since it has been shown to influence management in a significant proportion of cases, *e.g.* common variable immune deficiency (CVID), allergic bronchopulmonary aspergillosis (ABPA), and non-tuberculous mycobacterial (NTM) infection [8].

Definition of bronchiectasis

Patients with bronchiectasis usually complain of a chronic productive cough and recurrent lower respiratory tract infections. They often become breathless with exertion and complain of wheeze, although in most cases there is little variation in the airflow obstruction. Chest discomfort is common and they may have sharp pains or aching over the sites of the bronchiectasis. Chronic rhinosinusitis is common in all forms of bronchiectasis, but particularly when either impaired mucociliary clearance or immune deficiency are found to be the cause. Haemoptysis, which nowadays is seldom severe, occurs particularly during infective exacerbations. Tiredness is an important symptom to elicit, because it is often accepted by the patient as their "norm", and it is usually associated with poor disease control, and improves with treatment. Anxiety and depression may be present as in any chronic illness. It has been found that depression correlates with severity

of disease, but the level of anxiety may be higher than is appropriate [9]. Hereditary causes of bronchiectasis, such as cystic fibrosis and primary ciliary dyskinesia (PCD), exhibit symptoms from birth or soon after, whereas the majority of known causes have a variable age of onset. Exercise capacity, the frequency of exacerbations, requirement for hospitalisation, the presence or absence of *P. aeruginosa* infection and raised systemic markers of inflammation are the most important factors influencing quality of life in bronchiectasis [10].

Bronchiectasis results from the loss of structural proteins from the bronchial wall, such as elastin, and damage to the muscle and cartilage layers. Increased secretions are produced by goblet cell hyperplasia and hypertrophic sub-mucosal glands. Mucociliary clearance is impaired by loss of cilia due to epithelial damage, changes in mucus rheology, and pooling of secretions in dilated airways. Mucus plugging of small and large airways is common. Side branches of the tortuous airways are frequently lost, and small airways obliterated. Lymphocytes predominate in the bronchial wall, which contains lymphoid follicles, and neutrophils are abundant in the lumen. As well as B-lymphocytes, plasma cells and CD4 positive T-lymphocytes present in the follicles, there is a well-developed cell-mediated immune response, with increased numbers of activated T-lymphocytes, mainly of the suppressor/cytotoxic CD8 positive phenotype, antigen-processing cells and mature macrophages [11].

Bronchiectasis airways are dilated in a variety of ways: cylindrical or tubular bronchiectasis is the milder form and is most frequent, with uniform dilatation of the affected airway. Varicose bronchiectasis is more striking than cylindrical and local constrictions give this form an irregular outline to the airway (sometimes likened to a string of black pearls on HRCT images). Cystic or saccular bronchiectasis is the most severe form and the bronchi have a ballooned appearance. The HRCT criteria can be divided into major and ancillary signs (table 2). Airway dilatation is seen as a lack of normal tapering of an airway caught in its long axis; at right angles to this, a bronchiectatic airway has a diameter greater than the accompanying pulmonary artery (the so-called signet ring sign).

In a study of 91 patients with moderate-to-severe bronchiectasis followed up for 13 years, almost 30% died, 70% of these directly due to bronchiectasis, at a median age of 60 years [12]. Interestingly, an increase in the average right and left main pulmonary artery diameter (reflecting a degree of pulmonary arterial hypertension) was the strongest HRCT feature that predicted increased mortality [13]. Increased bronchial wall thickness and co-existing emphysema were other HRCT features predicting mortality in a multivariate analysis [12]. In a different longitudinal study, bronchial wall thickening and mucus plugging predicted future progression of disease [14].

Most patients have airflow obstruction of moderate severity and some gas trapping, with little reversibility, and preserved gas transfer. Deterioration in lung function over time is faster than the non-smoking population, ~50 mL per year. Frequent severe exacerbations and more systemic

Table 2. High-resolution computed tomography (CT) signs of bronchiectasis

Major signs
Bronchial dilatation
Non-tapering bronchi (in plane of CT section)
Diameter greater than accompanying pulmonary artery (perpendicular to CT section), the ''signet ring'' sign
Identification of peripheral bronchi (within 1 cm of pleural surface)
Mucus impaction within dilated bronchi
Ancillary signs
Bronchial wall thickening (NB. frequent feature of non-bronchiectatic conditions, *e.g.* asthma or viral lower respiratory tract infection)
Tree-in-bud pattern (reflecting inflammatory exudate in and around small airways)
Volume loss of affected lobe or segment
Mosaic attenuation pattern (accompanying obliterative bronchiolitis)
Interlobular septal thickening (mechanism unknown, not usually pronounced)

inflammation are associated with accelerated decline [15, 16]. Forced expiratory volume in 1 s (FEV_1) correlates with extent of bronchiectasis, degree of bronchial wall thickening and mosaic attenuation [14]. Improvement in FEV_1 most often corresponds with clearing of mucus plugging on HRCT rather than any conspicuous change in bronchial diameter. When a mosaic attenuation pattern (representing a component of obliterative small airways disease) becomes established, it does not regress. Airflow obstruction, particularly when there is also lung restriction, predicts increased mortality. This is also true for impaired gas transfer, which may be a signal of patients developing pulmonary hypertension [12].

Most patients have chronic bacterial colonisation of their bronchial mucosa even when they are well. The quality of life of patients is unchanged in the stable state whether the sputum cultured a potential bacterial pathogen or was sterile, although chronic infection with *P. aeruginosa* does impair quality of life. The effect of *P. aeruginosa* is not fully accounted for with this bacterium being associated with more severe disease. It is possibly because oral antibiotic options to treat exacerbations are more limited, so the treatment burden of inhaled antibiotic prophylaxis and hospital admission for intravenous antibiotics is greater [17]. The commonest isolate during exacerbations is non-typable *Haemophilus influenzae. P. aeruginosa* is associated with more extensive bronchiectasis, more severe airflow obstruction and a faster decline in FEV_1 [15, 18, 19]. Other species commonly cultured are *Staphylococcus aureus, Streptococcus pneumoniae, Moraxella catarrhalis, and* Gram-negative species such as *Stenotrophomonas maltophilia* and *Achromobacter* sp. Chronic infection with *S. aureus* has been associated with ABPA and cystic fibrosis, whilst isolation of *Burkholderia cepacia* suggests cystic fibrosis [20]. *Aspergillus* sp. may colonise bronchiectatic airways without necessarily causing infection or allergic responses. Similarly, NTM species may colonise and careful follow-up and investigation may be required to decide if they are pathogenic.

Aetiology of bronchiectasis

Clinical suspicion of bronchiectasis should lead to investigations to try to determine aetiology, and to assess extent of disease and functional impairment [21]. HRCT appearances may suggest the aetiology of the disease (table 3, figs 1–5). Two studies have looked at the prevalence of different aetiologies in fully investigated patients referred to tertiary centres [7, 8]. The results were similar, and a common diagnosis was idiopathic bronchiectasis (26–53%), which emphasises our lack of knowledge about the aetiology of many cases. Approximately one-third of patients were post infection. ABPA, CVID and PCD were the next most common (up to 10%). All other causes were $<4\%$, although it is our impression that NTM infection (a separate classification in the two studies) and aspiration are increasingly being recognised. A more recent study identified aetiology in a much larger proportion of cases, but this series included a much higher proportion of cases with positive autoimmune serology and haematological malignancy than the two UK series [22].

Structural lung conditions

Several types of congenital bronchiectasis occur because of absence or deficiency of elements of the bronchial wall that are crucial to its normal architecture. Tracheobronchomegaly (Mounier–Kuhn syndrome) is thought to be due to atrophy of the cartilage, elastic and muscular elements (fig. 2) [23], whereas in Williams–Campbell syndrome there is absence or markedly diminished amounts of cartilage in the subsegmental bronchi [24]. Bronchiectasis can also occur in Marfans and Ehlers–Danlos syndromes [11].

Localised bronchiectasis may occur distal to a bronchial obstruction from any cause. This can either be in the lumen, *e.g.* foreign body, tumour or broncholith [25, 26], or due to compression from outside, *e.g.* a lymph node [27], or due to constriction from scarring, *e.g.* sarcoidosis [28]. The obstruction impairs mucus clearance distally, making infection likely to occur, which sets up a chronic inflammatory condition that leads to bronchiectasis. Middle-lobe syndrome was originally

Table 3. Airways diseases with diagnostic or suggestive high-resolution computed tomography (HRCT) features

Near diagnostic HRCT	
ABPA	Upper lobe predominant varicose bronchiectasis (''string of black pearls'' sign) The density of mucus plugs may be strikingly higher than water density, a sign unique to ABPA
Cystic fibrosis	Whatever the severity of bronchiectasis, the degree of airway dilatation and bronchial wall thickening is more severe in the upper lobes than the lower lobes
Mounier–Kuhn syndrome (tracheobronchomegaly)	Characteristic massive dilatation of the trachea and main bronchi Grape-like saccular bronchiectasis (thin-walled) more distally, often with normal proximal and segmental bronchi
Diffuse panbronchiolitis	Generalised and uniform tree-in-bud pattern with relative sparing of the upper lobes Abnormalities of the segmental and subsegmental airways (either thickened or mildly bronchiectatic) are an invariable finding
Suggestive HRCT appearances	
NTM (specifically *Mycobacterium avium* complex)	Bronchiectasis is usually mild and relatively localised (often most severe in the middle lobes), scanty tree-in-bud pattern and scattered nodules (sometimes cavitating) are usually present If all features are present, HRCT is near diagnostic
α_1-AT deficiency-related bronchiectasis	Lower lobe cylindrical bronchiectasis on a background of panacinar emphysema (uniform ''black lung''); bronchiectasis tends to be mild
Post-viral constrictive obliterative bronchiolitis	Mosaic attenuation pattern conspicuous Within the areas of decreased attenuation lung, bronchiectasis of varying severity is present
Idiopathic bronchiectasis	The pattern of bronchiectasis tends to be cylindrical and lower lobe predominant; even when advanced and cystic, the upper lobe airways are relatively spared
Primary ciliary dyskinesia	Typically mid- and lower-zone bronchiectasis, sometimes conspicuously more severe in the middle lobes
Cartilage deficiency disorders (*e.g.* Williams–Campbell syndrome)	Delicate thin-walled bronchiectasis affecting subsegmental airways (the major airways are usually spared)

ABPA: allergic bronchopulmonary aspergillosis; NTM: non-tuberculous mycobacteria; α_1-AT: α_1-antitrypsin.

described by BROCK [29], and is caused when the right middle lobe is narrowed near its origin by extrinsic compression due to tuberculosis lymph nodes. The anatomy of the middle-lobe bronchus, which is narrow, long, acutely angulated and surrounded by a collar of lymph nodes at its origin, predisposes the lobe to infections if mucus clearance is impaired in any way. Patients present with recurrent pyrexial pneumonic illnesses, together with pleuritic chest pain, and consolidation is seen on the chest radiograph [11, 27]. There may be a similar explanation as to why the middle lobe is often the site of bronchiectasis occurring post-infection [11], in PCD [30] and in Lady Windermere syndrome, which is caused by infection by *Mycobacterium avium* complex [31]. In this latter syndrome, ineffective cough is thought to predispose to infection in middle-aged females.

Post infection

A severe infection of any sort can damage the bronchial wall sufficiently to cause bronchiectasis that is localised to the site of the infection. Globally, tuberculosis is the most common cause. The immature lung is particularly vulnerable, and whilst vaccination programmes have reduced their prevalence, childhood whooping cough and measles remain a relatively common cause of bronchiectasis. A diagnosis of post-infection bronchiectasis can be difficult to make because documentation of the original infection is absent. Patients may give a history of childhood infection when they present as adults with bronchial suppuration having not had any respiratory

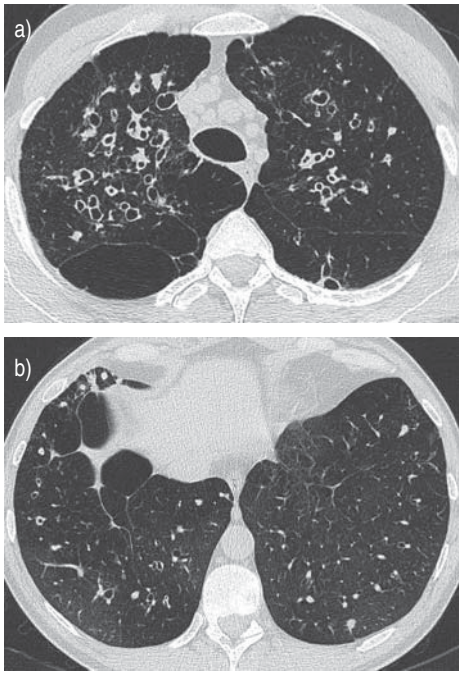

Figure 1. High-resolution computed tomography scan from a 22-year-old male with cystic fibrosis. a) Cylindrical bronchiectasis is visible in both upper lobes with a variable amount of mucus plugging and wall thickening of the affected airways. Occasional subpleural blebs and bullae are shown, but no pneumothorax. b) Mild cylindrical bronchiectasis in the lower lobes, typical of the upper lobe predominant distribution of bronchiectasis in cystic fibrosis.

Figure 2. A coronal computed tomography scan from a patient with Mounier–Kuhn syndrome (tracheobronchomegaly). In addition to the strikingly dilated trachea and main bronchi, the delicate thin-walled sacculations that characterise the bronchiectasis of Mounier–Kuhn syndrome are visible.

symptoms beforehand. Their HRCT shows more widespread disease than is likely from post infection, and the role, if any, of the childhood history remains speculative.

NTM are ubiquitous environmental organisms that may cause pulmonary disease in patients with chronic lung disease, and also some forms of immunodeficiency, *e.g.* HIV, but individuals with no apparent underlying predisposition may also develop infection by some species (*e.g. M. avium* complex *and Mycobacterium kansasii*) (fig. 3). Their prevalence is increasing [32]. *M. avium* complex is the most common cause of bronchiectasis [33, 34], and when this species infects established bronchiectasis of another cause it can lead to patients deteriorating and failing to respond to usual therapy. The presence of these environmental species in a sputum sample does not necessarily indicate disease. The two species described above, together with *Mycobacterium xenopi, Mycobacterium malmoense and Mycobacterium abscessus/chelonae* are the more pathogenic species, but careful observation and investigation over many months may be needed to decide that infection rather than colonisation is occurring. HRCT features, including progressive disease, are helpful in this regard.

Bronchiectasis is a common finding in Swyer–James (McLeod's) syndrome. Obliterative bronchiolitis most commonly follows a viral infectious insult to the developing lung during the first 8 years of life. Chest radiography shows a unilateral hyperinflated/hypovascular lung due to air trapping [35]. HRCT invariably reveals signs, albeit much less severe, of obliterative bronchiolitis in the contralateral lung.

Immunodeficiency

Primary immunodeficiency disorders comprise many diseases caused by genetic defects affecting the immune system. CVID is the most common, and is characterised by low serum antibody levels, poor antibody responses and recurrent bacterial infections. There is a bimodal age of presentation, either in early childhood, or in the second or third decade of life. Pneumonia is the most common presenting feature. Recurrent pneumonia should always lead to suspicion of an underlying immunodeficiency. Rhinosinusitis and bronchitis are more common than pneumonia, but because they are less serious conditions the possibility of CVID is only considered when the conditions are more severe and chronic. The majority of CVID patients develop post-infection bronchiectasis, particularly when diagnosis is delayed. Other common infectious complications of CVID include

otitis media, giardia, *Campylobacter* and *Salmonella enteritis*, and cutaneous herpes zoster [36]. Solitary IgA deficiency occurs in 0.1–0.2% of the population and can be present without any associated clinical problems, although some patients experience frequent viral-like illnesses. Polysaccharide antibody responses predominantly lie in IgA and IgG2 subclass. Impaired responses to pneumococcal vaccination identify a group of patients who are susceptible to infections with encapsulated bacteria and may develop bronchiectasis for this reason. This may sometimes be linked to IgA deficiency. Some of these patients may develop CVID later in life [11].

Figure 3. A high-resolution computed tomography scan showing *Mycobacterium avium* complex infection in a 64-year-old female. The typical triad of: 1) mild localised bronchiectasis in the right upper lobe, 2) associated ''tree-in-bud'' pattern, and 3) small cavitating nodule in the apical segment of the right lower lobe can be seen.

X-linked agammaglobulinaemia is a much rarer immune deficiency caused by a mutation in an enzyme critical for the expansion of pre-B-lymphocytes leading to a complete absence of the B-lymphocyte system [36]. Children with other severe immune deficiencies often do not survive, but develop bronchiectasis before they die. Defects of neutrophil function, such as adhesion, respiratory burst and chemotaxis are rare causes of bronchiectasis, but can present for the first time in adult life. More severe immunodeficiencies will usually have a history of infections at multiple sites [37, 38].

Acquired antibody deficiency occurs in a number of conditions including multiple myeloma, chronic lymphocytic leukaemia, protein-losing enteropathy, nephrotic syndrome and lymphoma. Antibody deficiency may also occur following bone marrow transplantation, cytotoxic therapy for malignancy and novel monoclonal antibody therapies that target B-lymphocytes in autoimmune disease, *e.g.* rituximab for rheumatoid arthritis. Patients with secondary antibody deficiency are prone to the same lung infections as CVID, although many have more complicated immunodeficiency with additional abnormality in cellular immunity, so they may also present with opportunistic infections more typical of T-lymphocyte disorders [36]. Bronchiectasis can also complicate HIV, and this may be seen more frequently because of improved survival with antiretroviral therapy [11].

Allergic bronchopulmonary aspergillosis

Aspergillus species are ubiquitous in the environment. *A. fumigatus* is by far the commonest species causing human disease, but other species are recognised as well. They are typically found in moist areas of decaying organic matter, but can also be cultured from indoor sources such as house dust and air-conditioning units. ABPA occurs more commonly in wet climates that are not cold, and spore levels are higher during wet times of the year. ABPA can cause bronchiectasis or can complicate established bronchiectasis from another cause (fig. 4) [11]. Primary ABPA typically affects the proximal bronchial tree and the upper lobes, although this classic distribution is not always present [39]. It is caused by an immune reaction involving eosinophils to fungal spores colonising the airways. Atelectasis occurs because of obstruction by plugs of inspissated secretions containing fungal hyphae. Acute episodes are characterised by fever, wheeze, expectoration

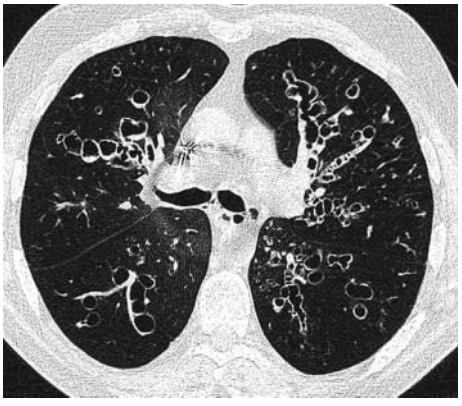

Figure 4. Allergic bronchopulmonary aspergillosis in an asthmatic patient. High-resolution computed tomography scan through the mid zones showing proximal varicose bronchiectasis (''string of black pearls'' sign). The lower lobe bronchi were relatively normal.

Figure 5. Diffuse panbronchiolitis in a 42-year-old male with sino-bronchial sepsis. The widespread micronodules and tree-in-bud pattern signify exudate in and around the small airways. Cylindrical bronchiectasis usually accompanies diffuse panbronchiolitis (in this case mild). There are healed cough fractures on the left of the scan.

of viscid sputum plugs and pleuritic chest pain. Fleeting consolidation is typical on serial chest radiographs. However, as bronchiectasis develops, a chronic picture evolves over time with daily purulent sputum production, and exacerbations of ABPA are then difficult to distinguish from infective exacerbations of bronchiectasis. The levels of serum IgE and specific *Aspergillus* radioallergosorbent test help determine the allergic component, but in many cases the inflammation is a mixture of allergic/infective.

It has been reported that there is a higher prevalence of *Aspergillus* lung disease in patients with NTM compared to other forms of bronchiectasis [40]. The possibility of the two conditions co-existing should be kept in mind. The reasons might be: a common host defence abnormality involving the interferon (IFN)-γ pathway; reduced host defence caused by frequent antibiotic and steroid treatment; or damage caused by one agent allowing colonisation by the other.

Abnormal mucociliary clearance

Mucociliary clearance is a first-line defence mechanism that protects epithelial surfaces against inhaled particles including bacteria. Particles are trapped in the mucus layer which is transported to the back of the throat by ciliary beating. The system malfunctions for different reasons in these three conditions, leading to recurrent bacterial infections that become chronic as the condition deteriorates and bronchiectasis develops.

In PCD, neonates can present with respiratory distress. Cilia are hair-like structures found on the cell surface in the nose and paranasal sinuses, middle ear, Eustachian tubes, bronchial tree, fallopian tubes and brain ventricles. Sperm tails are modified cilia. Cilia should be examined in all children with bronchiectasis for which another cause has not been found. In adults, respiratory symptoms dating from childhood, infertility and/or dextrocardia, and severe chronic rhinosinusitis/history of middle ear problems are reasons to investigate ciliary function. Their coordinated beating, between 11 and 16 Hz, is the driving force of the mucociliary system. The incidence of PCD is estimated at between one in 15,000 to 30,000 births. Multiple genetic defects can cause PCD, which can result in situs inversus, dextracardia and infertility. However, the main clinical problems are repeated upper and lower respiratory tract infections with bronchiectasis, and chronic otitis media causing loss of hearing. Cilia may be immotile, but in other cases have slow uncoordinated movement and their orientation on the cell surface may be disorganised. In many cases electron microscopy reveals an abnormality of the ultrastructure of the cilia, the most common of which is absence of one or both dynein arms, which contain ATPase to provide energy for beating. A small number of cases have normal ultrastructure, and the cause of the PCD is uncertain, but may be beyond the resolution of the electron microscope [41, 42].

Cystic fibrosis is a multisystem disorder caused by genetic mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR), a cyclic-AMP dependent chloride channel, which has wide-ranging effects including decreasing airway surface fluid that impairs mucociliary clearance. Most patients present in early life and are treated in specialist units. However, milder cases, due to rarer gene mutations, may present in adults. There should be a low threshold for investigating the possibility of cystic fibrosis in younger patients with bronchiectasis. The clues to the diagnosis are: history from childhood; the distribution of disease on HRCT (fig. 1a and b); and sputum bacteriology, *S. aureus* (often with *P. aeruginosa*) and *B. cepacia* [11, 20]. There is emerging literature suggesting abnormal epithelial cell ion transport as a possible

aetiological factor in patients with idiopathic bronchiectasis; however, as yet the significance of these reports is uncertain [43, 44].

Young's syndrome comprises the triad bronchiectasis, chronic sinusitis and azoospermia due to a functional blockage of sperm in the caput epididymis, which is usually enlarged and palpable in the scrotum. The cause of the condition is unknown and it may present late in life after successful parenthood. The sputum is abnormally viscid making it difficult to clear by ciliary beat and coughing [45]. The syndrome has been linked to mercury poisoning in childhood (Pink disease), which used to occur before calomel (mercury (I) chloride) was removed from teething powders and worm medication [46]. An equivalent Young's syndrome is recognised in females who had mercury poisoning in childhood.

Systemic diseases

An association between bronchiectasis and autoimmune disease is well recognised, and is detected more frequently with the advent of HRCT being used to diagnose and monitor interstitial lung disease. However, bronchiectasis may occur for reasons other than the autoimmune disease itself which directly causes bronchiectasis by weakening the bronchial wall [47]. Connective tissue diseases involving the lung are frequently associated with pulmonary fibrosis. As a consequence of established parenchymal fibrosis underlying airways are distorted and dilated (traction bronchiectasis). The airway mucosa is normal with intact mucociliary clearance and, possibly for this reason, the dilated airways are not prone to bacterial infections. Traction bronchiectasis is common in lung involvement with scleroderma but is usually asymptomatic [47]. Severe or recurrent infections may be predisposed to by immunosuppression due to the autoimmune disease itself or its treatment, making the aetiology of the bronchiectasis post-infection rather than a direct relationship to the autoimmune disease. Autoimmune disease directly causing bronchiectasis is best described in rheumatoid arthritis, and obliterative bronchiolitis is usually a prominent feature of these cases. The prevalence of bronchiectasis in rheumatoid arthritis involving the lung varies widely in different studies, but may be present in up to half of cases [47–49]. The presence of bronchiectasis with rheumatoid arthritis overall seems to lead to a worse prognosis [47], although this has only been addressed directly in one study [49]. Other causes of constrictive obliterative bronchiolitis in which there is accompanying bronchiectasis include post-viral obliterative bronchiolitis, graft-*versus*-host disease and transplant rejection [11].

Bronchiectasis is associated with ulcerative colitis [50], Crohn's disease [51] and coeliac disease [52]. This may be related to the lung and bowel sharing a common immune system with cells migrating between the two sites. The association with ulcerative colitis is best characterised. The classic presentation is that a patient who has had severe colitis, but has never had any respiratory symptoms, eventually comes to total colectomy then develops abrupt onset of cough and purulent sputum production soon afterwards. These patients characteristically produce very large volumes of purulent, but sterile, sputum. In other cases the bronchiectasis may be unrelated to colectomy. Patients with one condition develop the other at a different time-point. Flare-ups in the bowel disease may or may not be associated with exacerbations of lung symptoms, but their respiratory symptoms usually improve when they are given systemic corticosteroids for their colitis. Both ulcerative colitis and bronchiectasis are negatively correlated with cigarette smoking [11].

The association of Crohn's disease and coeliac disease with bronchiectasis is less well described. The onset of cough and sputum production has also been linked to bowel resection in Crohn's disease [51]. Both coeliac disease and bronchiectasis have an infiltrate of T-cells in the mucosa, which has led to speculation that some cases of idiopathic bronchiectasis may have sub-clinical coeliac disease [53].

Yellow nail syndrome is rare, and involves yellow discolouration of dystrophic nails, primary lymphoedema and chylous pleural effusions [54]. Rhinosinusitis is common [55], and a proportion of cases have bronchiectasis. The prevalence of bronchiectasis in the syndrome is unknown, but may be less than half of cases [56].

Toxic damage

Inhalation of toxic gases, *e.g.* ammonia or smoke in survivors of fire accidents, particularly damages the small airways causing constrictive obliterative bronchiolitis and can also cause bronchiectasis [57]. Aspiration of swallowed matter and/or gastric contents, which may occur because of reduced conscious level or in neuromuscular conditions, can lead to bronchiectasis, particularly if it is accompanied by microbial infection [58]. Acid reflux is very common in the general population, usually due to a hiatus hernia, and aspiration leads to bronchitis with cough, wheeze and sputum production. Whether acid reflux alone can cause bronchiectasis is presently speculative.

Obstructive airways diseases

HRCT features of asthma range from normal through to bronchial wall thickening of variable severity, and finally overt bronchiectasis. The prevalence has varied widely in different studies, partly because of the criteria used to categorise patients [59], but in a study using criteria to define frank bronchiectasis it was present in 29% of asthmatic patients [60]. The changes may be more conspicuous in the upper lobes, and have been related to the length of the asthma history [61–63]. A direct link between bronchiectasis and the severity of the asthma has not been established [60], and the changes can reverse [64]. The pathogenesis of these bronchial abnormalities and their clinical relevance remain unknown. Chronic inflammation of the airways probably leads to some morphological remodelling of the airways with dilatation being one feature, whilst an increase in several components of the bronchial wall, including smooth muscle hypertrophy, also occur [65].

Some studies have suggested that the prevalence of bronchiectasis in COPD is quite common [4, 5], but more studies are required, particularly in unselected patients from primary care. The aetiology may relate to post-infection damage, but the diffuse nature of the disease in some cases suggests that chronic neutrophilic inflammation, which is common to both diseases, might be responsible [11, 66]. The clinical relevance of bronchiectasis, particularly with respect to susceptibility to infective exacerbations and chronic infection by *P. aeruginosa* needs further investigation [67]. In one study of a cohort of severe COPD patients, in whom overt bronchiectasis was an exclusion factor at the outset, bronchiectasis was present in 50%, usually mild tubular disease in the lower lobes. The presence of bronchiectasis was associated with more severe exacerbations, slower recovery, lower airway bacterial colonisation and higher levels of airway inflammation [4].

α_1-antitriypsin deficiency leads to emphysema, particularly in cigarette smokers. In one study of severe deficiency most (70 out of 74) patients had some bronchiectasis on HRCT, and it was felt to be clinically relevant in 27%. There was also a correlation between airflow obstruction and bronchial wall thickness [68]. In another study of 150 adult bronchiectasis patients no PiZZ individuals were found nor was there any increase in the frequency of partial deficiency phenotypes [7], a finding confirmed in a separate study [69]. Therefore, it seems that absence of α_1-antitriypsin disturbs the protein–anti-protease balance to cause bronchiectasis in some cases as well as emphysema, but that this is not the case with partial deficiency.

Diffuse panbronchiolitis was first described in Japan, and subsequently in Korea and China, but is a rare presentation of bronchiectasis in Caucasian populations [8, 70–72]. Patients usually present in middle age or older, and have sinusitis, dyspnoea and a productive cough. Inflammation causes hypertrophy of the wall of the respiratory bronchioles, and involves infiltration with plasma cells, lymphocytes and foamy cells. The characteristic HRCT feature of a diffuse tree-in-bud pattern progresses to bronchiectasis if untreated (fig. 5).

Idiopathic bronchiectasis

We remain ignorant about the aetiology of bronchiectasis in up to half of cases. A ''vicious cycle'' hypothesis of bacteria driven, host-mediated damage to the bronchial tree was proposed by Prof.

Peter Cole over 30 years ago to explain the pathogenesis of bronchiectasis [73]. This hypothesis has stood the test of time, and remains the best model for considering causes and management of bronchiectasis. Impaired defences permit bacteria that are inhaled or aspirated into the bronchial tree to persist and multiply establishing chronic infection. Neutrophils are attracted to the airways from the circulation by bacterial products and host mediators. Chronic neutrophilic inflammation damages tissue *via* spillage of protease enzymes and reactive oxygen species which overwhelm the body's ability to neutralise them. Tissue damage further impairs the host defences propagating the circle. Different aetiologies enter the circle at different points, as illustrated in figure 6.

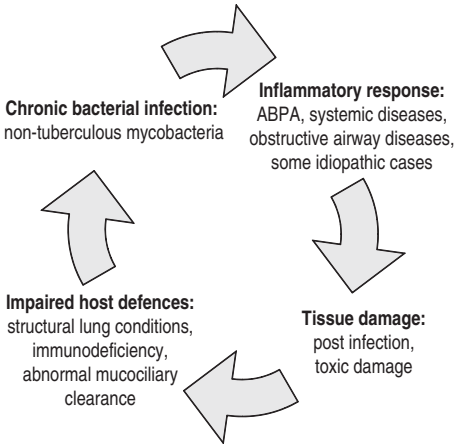

Figure 6. A vicious circle of chronic bacterial infection and inflammation that causes tissue damage in bronchiectasis. The aetiologies of bronchiectasis enter the circle at different points. ABPA: allergic bronchopulmonary aspergillosis.

Post-infective bronchiectasis, shown on HRCT and defined as symptoms of bronchiectasis which followed immediately after an identified infective illness, has been compared to a group of idiopathic patients who have undergone full investigation to exclude known causes [8]. There was a female predominance in both groups. Idiopathic patients commonly presented in their 30s and 40s, whereas the post-infection group was younger because of the number of childhood cases. The bronchiectasis in the idiopathic group was usually tubular, bilateral, of lower lobe predominance and symmetrical, whilst the site of post-infection disease was more varied. Chronic rhinosinusitis was prominent in most idiopathic cases compared to only half of post infection, which might infer an underlying abnormality in idiopathic cases affecting the whole of the respiratory tract. Idiopathic cases sometimes described an acute illness at the onset of their symptoms which never completely resolved, or the productive cough may have arisen without an obvious cause. Whichever history they presented with, the symptoms were usually chronic from the outset; whereas the post-infection group were often intermittent, at least until chronic bronchial infection occurred. It seems likely that fresh aetiologies of bronchiectasis will be discovered, but one possible explanation of some idiopathic cases may be dysregulation of the inflammatory response to various stimuli. Microbial infection is likely to be involved, and an exuberant inflammatory response, which does not switch off in the usual manner when the infection is overcome, could cause tissue damage leading into the vicious circle [74].

Statement of Interest

None declared.

References

1. Weycker D, Edelsberg J, Oster G, *et al.* Prevalence and economic burden of bronchiectasis. *Clin Pulm Med* 2005; 12: 205–209.
2. Säynäjäkangas O, Keistinen T, Tuuponen T, *et al.* Bronchiectasis in Finland: trends in hospital treatment. *Respir Med* 1997; 9: 395–398.
3. Twiss J, Metcalfe R, Edwards E, *et al.* New Zealand national incidence of bronchiectasis "too high" for a developed country. *Arch Dis Child* 2005; 90: 737–740.
4. Patel IS, Vlahos I, Wilkinson TM, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400–407.
5. O'Brien C, Guest PJ, Hill SL, *et al.* Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635–642.
6. Wilson R. Bronchiectasis and COPD. *In:* Stockley RA, Rennard SI, Rabe K, *et al.* eds. *Chronic Obstructive Pulmonary Disease: A Practical Guide to Management*. Oxford, Blackwell Publishing, 2007; pp. 139–147.
7. Pasteur MC, Helliwell SM, Houghton SJ, *et al.* An investigation into causative factors in patients with bronchiectasis. *Am J Respir Crit Care Med* 2000; 162: 1277–1284.

8. Shoemark A, Ozerovitch L, Wilson R. Aetiology in adult patients with bronchiectasis. *Respir Med* 2007; 101: 1163–1170.
9. O'Leary CJ, Wilson CB, Hansell DM, *et al.* Relationship between psychological well-being and lung health status in patients with bronchiectasis. *Respir Med* 2002; 96: 686–692.
10. Wilson CB, Jones PW, O'Leary CJ, *et al.* Health status assessment in bronchiectasis using the St George's Respiratory Questionnaire. *Am J Respir Crit Care Med* 1997; 156: 536–541.
11. Wilson R. Bronchiectasis. *In:* Gibson JG. Geddes DM, Costobel A, *et al.* eds. Respiratory Medicine. 3rd Edn. *Volume 2*. Edinburgh, Saunders, 2003; pp. 1445–1464.
12. Loebinger MR, Wells AU, Hansell DM, *et al.* Mortality in bronchiectasis: a long-term study of the factors influencing survival. *Eur Respir J* 2009; 34: 843–849.
13. Deveraj A, Wells AU, Meister MG, *et al.* Pulmonary hypertension in patients with bronchiectasis: prognostic significance of CT signs. *AJR Am J Roentgenol* 2011; 196: 1300–1304.
14. Sheehan RE, Wells AU, Copley SJ, *et al.* A comparison of serial computed tomography and functional change in bronchiectasis. *Eur Respir J* 2002; 20: 581–587.
15. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, *et al.* Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007; 132: 1565–1572.
16. King PT, Holdsworth SR, Freezer NJ, *et al.* Outcome in adult bronchiectasis. *COPD* 2005; 2: 27–34.
17. Wilson CB, Jones PW, O'Leary CJ, *et al.* Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J* 1998; 12: 820–824.
18. Evans SA, Turner SM, Bosch BJ, *et al.* Lung function in bronchiectasis: the influence of *Pseudomonas aeruginosa*. *Eur Respir J* 1996; 9: 1601–1604.
19. Miszkiel KA, Wells AU, Rubens MB, *et al.* The effects of airway colonization by *Pseudomonas aeruginosa*: a CT study. *Thorax* 1997; 52: 260–264.
20. Shah PL, Mawdsley S, Nash K, *et al. Staphylococcus aureus* in patients with bronchiectasis; identification of disease associations. *Eur Respir J* 1998; 12: 1340–1344.
21. Pasteur MC, Bilton D, Hill AT. Guideline for non-CF bronchiectasis. *Thorax* 2010; 65: 1–58.
22. McShane PJ, Naureckas ET, Strek ME. Bronchiectasis in a diverse US population. *Chest* 2012; 142: 159–167.
23. Gay S, Dee P. Tracheobronchomegaly: the Mounier-Kuhn syndrome. *Br J Radiol* 1984; 57: 640–644.
24. Jones VF, Eid NS, Franco SM, *et al.* Familial congenital bronchiectasis: Williams-Campbell Syndrome. *Pediatr Pulmonol* 1993; 16: 263–267.
25. Conces DJ Jr, Tarver RD, Vix VA. Bronchiolithasis: CT features in 15 patients. *AJR Am J Roentgenol* 1991; 157: 249–253.
26. Zissin R, Shapiro-Feinberg M, Rozenman J, *et al.* CT findings of the chest in adults with aspiration foreign bodies. *Eur Radiol* 2001; 11: 606–611.
27. Kwon KY, Myers JL, Swensen SJ, *et al.* Middle lobe syndrome: a hyperlucent lung syndrome: a clinicopathological study of 21 patients. *Hum Pathol* 1995; 26: 302–307.
28. Udwadia ZF, Pilling JR, Jenkins PF, *et al.* Bronchoscopic and bronchographic findings in 12 patients with sarcoidosis and severe progressive airways obstruction. *Thorax* 1990; 45: 272–275.
29. Brock RC. Post-tuberculous broncho-stenosis and bronchiectasis of the middle lobe. *Thorax* 1950; 5: 5–39.
30. Nadel HR, Stringer DA, Levison H, *et al.* The immotile cilia syndrome: radiological manifestations. *Radiology* 1985; 154: 651–655.
31. Reich JM, Johnson RE. *Mycobacterium avium* complex pulmonary disease presenting as an isolated lingula or middle lobe pattern: the Lady Windermere Syndrome. *Chest* 1992; 101: 1605–1609.
32. Winthrop KL, McNelley E, Kendall B, *et al.* Pulmonary nontuberculous mycobacterial disease prevalence and clinical features; an emerging public health disease. *Am J Respir Crit Care Med* 2010; 182: 977–982.
33. Wickremasinghe M, Ozerovitch LJ, Davies G, *et al.* Non-tuberculous mycobacteria in patients with bronchiectasis. *Thorax* 2005; 60: 1045–1051.
34. Fowler SJ, French J, Screaton NJ, *et al.* Nontuberculous mycobacteria in bronchiectasis: prevalence and patient characteristics. *Eur Respir J* 2006; 28: 1204–1210.
35. Lucaya J, Gartner S, Garcia-Pena P, *et al.* Spectrum of manifestations of Swyer-James-MacLeod syndrome. *J Comput Assist Tomogr* 1998; 22: 592–597.
36. Webster ADB. Humoral immunodeficiency and the lung. *In:* Verleden GM, Demedts MG, Westhovens R, *et al.* eds. Pulmonary Manifestations of Systemic Diseases. *Eur Respir Monogr* 2006; 34: 220–233.
37. Vendrell M, de Gracia J, Rodrigo MJ, *et al.* Antibody production deficiency with normal IgG levels in bronchiectasis of unknown etiology. *Chest* 2005; 127: 197–204.
38. Fried AJ, Bonilla FA. Pathogenesis, diagnosis and management of primary antibody deficiencies and infections. *Clin Microbiol Rev* 2009; 22: 396–414.
39. Reiff DB, Wells AU, Carr DH, *et al.* CT findings in bronchiectasis: limited value in distinguishing between idiopathic and specific types. *AJR Am J Roentgenol* 1995; 165: 261–267.
40. Kunst H, Wickremasinghe M, Wells A, *et al.* Nontuberculous mycobacterial disease and aspergillus-related lung disease in bronchiectasis. *Eur Respir J* 2006; 28: 352–357.
41. Bush A, Cole P, Hariri M, *et al.* Primary ciliary dyskinesia diagnosis and standards of care. *Eur Respir J* 1998; 12: 982–988.

42. Noone P, Leigh M, Sannuti A, *et al.* Primary ciliary dyskinesia: diagnostic and phenotype features. *Am J Respir Crit Care Med* 2004; 169: 459–467.
43. Bienvenu T, Sermet-Gaudelus I, Burgel PR, *et al.* Cystic fibrosis transmembrane conductance regulator channel dysfunction in non cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2010; 181: 1078–1084.
44. Fajac I, Viel M, Sublemontier S, *et al.* Could a defective epithelial sodium channel lead to bronchiectasis. *Respir Res* 2008; 9: 46–54.
45. Handelsman DJ, Conway AJ, Boylan LM, *et al.* Young's syndrome. Obstructive azoospermia and chronic sinopulmonary infections. *N Engl J Med* 1984; 310: 3–9.
46. Hendry WF, A'Hern RP, Cole PJ. Was Young's syndrome caused by exposure to mercury in childhood? *Br Med J* 1993; 307: 1579–1582.
47. Dhasmana DJ, Wilson R. Bronchiectasis and autoimmune disease. *In:* Floto RA, Haworth CS, eds. *Bronchiectasis.* Eur Respir Monogr 2011; 52: 192–210.
48. Mohd Noor N, Mohd Shahrir MS, Shahid MS, *et al.* Clinical and high resolution computed tomography characteristics of patients with rheumatoid arthritis lung disease. *Int J Rheum Dis* 2009; 12: 136–144.
49. Devouassoux G, Cottin V, Lioté H, *et al.* Characterisation of severe obliterative bronchiolitis in rheumatoid arthritis. *Eur Respir J* 2009; 33: 1053–1061.
50. Rutland RJA, Cole PJ, Citron KM, *et al.* Chronic bronchial suppuration and inflammatory bowel disease. *Q J Med* 1981; 50: 63–75.
51. Eaton TE, Lambie N, Wells AU. Bronchiectasis following colectomy for Crohn's disease. *Thorax* 1998; 53: 527–531.
52. Mahadeva R, Flower C, Shneerson J. Bronchiectasis in association with coeliac disease. *Thorax* 1998; 53: 527–529.
53. Stockley RA. Bronchiectasis and inflammatory bowel disease. *Thorax* 1998; 53: 526–527.
54. Maldonado F, Tazelaar H, Wang C, *et al.* Yellow nail syndrome: analysis of 41 consecutive patients. *Chest* 2008; 134: 375–381.
55. Hershko A, Hirshberg B, Nahir M, *et al.* Yellow nail syndrome. *Postgrad Med J* 1977; 73: 466–468.
56. Hiller E, Rosenow EC, Olsen AM. Pulmonary manifestations of the yellow nail syndrome. *Chest* 1972; 61: 452–458.
57. Hoeffler HB, Schweppe I, Greenberg SD. Bronchiectasis following pulmonary ammonia burn. *Arch Pathol Lab Med* 1982; 106: 686–687.
58. Warnock ML, Ghahremani CG, Rattenborg C, *et al.* Pulmonary complications of heroin intoxication: aspiration pneumonia and diffuse bronchiectasis. *JAMA* 1972; 219: 1051–1053.
59. Diseases of the airways. *In*: Hansell DM, Lynch DA, McAdams HP, *et al.* eds. Images of Disease of the Chest. Elsevier, 2010; pp. 715–785.
60. Grenier P, Mourey-Gerosa I, Benali K, *et al.* Abnormalities of the airways and lung parenchyma in asthmatics: CT observations in 50 patients and inter- and intra-observer variability. *Eur Radiol* 1996; 6: 199–206.
61. Awadh N, Muller NL, Park CS, *et al.* Airway wall thickness in patients with near fatal asthma and control groups: assessment with high resolution computed tomographic scanning. *Thorax* 1998; 53: 248–253.
62. Shiba K, Kasahara K, Nakajima H, *et al.* Structural changes of the airway wall impair respiratory function even in mild asthma. *Chest* 2002; 122: 1622–1626.
63. Gupta S, Siddiqui S, Haldar P, *et al.* Qualitative analysis of high resolution CT scans in severe asthma. *Chest* 2009; 136: 1521–1528.
64. Cukier A, Stelmach R, Kavakama JI, *et al.* Persistent asthma in adults: comparison of high resolution computed tomography of the lungs after one year of follow-up. *Rev Hosp Clin Fac Med Sao Paulo* 2001; 56: 63–68.
65. Niimi A, Mastumoto H, Takemura M, *et al.* Clinical assessment of airway remodelling in asthma: utility of computed tomography. *Clin Rev Allergy Immunol* 2004; 27: 45–58.
66. Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000; 343: 269–280.
67. Murphy TF, Brauer AL, Eschberger K, *et al. Pseudomonas aeruginosa* in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177: 852–860.
68. Parr DG, Guest PG, Reynolds JH, *et al.* Prevalence and impact of bronchiectasis in alpha 1-antitrypsin deficiency. *Am J Respir Crit Care Med* 2007; 176: 1215–1222.
69. Cuvelier A, Muir JF, Hellot MF, *et al.* Distribution of α1-antitrypsin alleles in patients with bronchiectasis. *Chest* 2000; 117: 415–419.
70. Homma H, Yamanake A, Tanimoto S, *et al.* Diffuse panbronchiolitis. A disease of the transitional zone of the lung. *Chest* 1983; 83: 63–69.
71. Nishimura K, Kitaichi M, Izumi T, *et al.* Diffuse panbronchiolitis: correlation of high-resolution CT and pathologic findings. *Radiology* 1992; 184: 779–785.
72. Hoiby N. Diffuse panbronchiolitis and cystic fibrosis: East meets West. *Thorax* 1994; 49: 531–532.
73. Cole PJ. A new look at the pathogenesis and management of persistent bronchial sepsis: a vicious circle hypothesis and its logical therapeutic connotations. *In*: Davies RJ, ed. Strategies for the management of chronic bronchial sepsis. Oxford, Medicine Publishing Foundation, 1984: 1–20.
74. Boyton RJ, Smith J, Ward R, *et al.* HLA-C and killer cell immunoglobulin-like receptor genes in idiopathic bronchiectasis. *Am J Respir Crit Care Med* 2006; 173: 327–333.

Chapter 12

The role of inhaled antibiotics in bronchial infection

Diana Bilton

SUMMARY: Inhaled antibiotics are a useful tool in the management of chronic infection with *Pseudomonas aeruginosa* in the setting of cystic fibrosis (CF). Large randomised trials in CF have given us insight into the relationships between antimicrobial efficacy and clinical outcomes. The evidence base is now being expanded to non-CF bronchiectasis as new antibiotic formulations are developed and clinical trials performed. In the next few years we expect to see specific inhaled antibiotic preparations licenced for use in non-CF bronchiectasis. The challenges ahead are to identify the best regimens that produce the best efficacy whilst limiting production of antibiotic resistance.

KEYWORDS: Bronchiectasis, cystic fibrosis, inhaled antibiotic, *Pseudomonas aeruginosa*

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Eur Respir Monogr 2013; 60: 120–126.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10018112
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

In the presence of chronic airway infection where antibiotic therapy may be required either on a recurrent or persistent basis, the inhaled route provides an attractive alternative to oral agents. As chronic bronchial sepsis requires a high dose of antibiotics *via* the enteral or parenteral route to achieve reasonable sputum levels, the direct inhalational route allows high doses of antimicrobials to be achieved in the airway by direct administration with negligible systemic exposure and associated reduction in risks of toxicity [1–3]. The limitation to this route largely relates to tolerability, which appears to differ between disease groups.

In addition, recent concerns regarding the increase in *Clostridium difficile* infection in patients receiving systemic antibiotics is a powerful driver for examining alternative routes of administration to avoid exposure of the gastrointestinal tract to high levels of broad-spectrum antimicrobial therapy.

Inhaled antibiotics in cystic fibrosis

Development of the inhaled route was driven in cystic fibrosis (CF) by the requirement to treat chronic infection with *Pseudomonas aeruginosa*. *Staphylococcus aureus* and *Haemophilus influenza*, common organisms in children with CF, provide less of a therapeutic challenge because of the range of clinically effective oral therapies with good airway penetration. Aerosolised antibiotic

therapy focussed on treatment of *P. aeruginosa* as a result of the lack of oral agents with good activity against the organism (ciprofloxacin being the sole useful agent), and the requirement for prolonged and/or repeated use. Aerosolised administration of antibiotics has become the standard of care in the management of *Pseudomonas* infection in CF [1]. The aim of treatment has been to reduce the burden of infection by reducing bacterial numbers, thus improving lung function and reducing exacerbations.

Despite many years of clinical experience with inhaled colistin in Europe, a review of the evidence base reveals a paucity of data for its use from randomised controlled clinical trials in patients with CF. The long-term use of nebulised colistin was based on a small study from Denmark revealing a reduction in the decline in lung function following a course of intravenous antibiotics [4]. HODSON *et al.* [5] reported the improvement in lung function following a combination of carbenicillin and gentamicin. These and other earlier studies were reviewed by MUKHOPADHYAY *et al.* [6], and the principal of long-term chronic suppressive therapy for *P. aeruginosa* infection in order to maintain lung function and reduce exacerbations was widely accepted in Europe. Twice daily therapy with a nebulised antibiotic every day of the year became recommended therapy and the use of colistin predominated because of the general acknowledgement that although long-term use in chronic infection was likely to promote antibiotic resistance, colistin resistance was rare. Furthermore, colistin was not in routine use for *i.v.* therapy in CF.

The development of preparations specifically designed by pharmaceutical companies for inhalational use, the first being TOBI® (tobramycin 300 mg in 5 mL solution; Novartis, Basel, Switzerland), resulted in large multicentre, randomised trials preceded by appropriate animal toxicology studies (something that had been absent from previous clinician led studies). The Ramsey study in 1999 [7] remains a landmark study, setting the gold standard for future studies to gain regulatory approval for chronic administration of a nebulised antibiotic in CF. The 6-month study included 520 patients and demonstrated significant improvement in forced expiratory volume in 1 s (FEV_1) compared to placebo and a reduction in pulmonary exacerbations requiring rescue *i.v.* antibiotics. The improvement in lung function was mirrored by a reduction in bacterial numbers. The new departure was the concept of cycles of therapy, administering twice daily therapy for a 28-day period followed by a 28-day cycle free of antibiotic therapy. The rational was based on previous studies showing maximal clinical efficacy within the 28-day period and the belief that the lack of persistent daily therapy would reduce the development of resistant organisms [8]. Thus, 1999 proved the watershed for trials of nebulised antibiotics for chronic therapy in CF.

The paradigm of an acute intervention with antibiotic therapy to kill and eradicate the infecting organism does not fit well when considering chronic airway disease. Once chronic airway infection is established eradication of the organism is unlikely and so development of resistance may become a concern.

Whilst the mode of action of an inhaled antibiotic is thought to be largely antibacterial, the key outcome measures for phase III trials of chronic therapy are clinical, *i.e.* improvement in lung function or a reduction in requirement for additional antibiotics for acute exacerbations of infection. A signal of reduction in bacterial numbers is, however, expected in proof-of-concept studies and was certainly demonstrated in the Ramsey study [7]. It is of interest that in the first month of treatment numbers of *P. aeruginosa* dropped by an average of 2 $\log_{10}$ CFU per mL but as the trial continued and the monthly cycles were repeated the effect on bacterial numbers diminished despite a better preserved effect on lung function. This raised the interesting debate of a possible beneficial but non-bacterial killing effect of the inhaled drug.

Microbiological end-points other than bacterial numbers remain important because of safety concerns regarding the long-term use of antibiotic therapy. Thus, the promotion or prevention of resistance to antibiotics is a key consideration. It is clear that resistance *in vitro* does not correlate with clinical response to an aerosolised antibiotic, as shown in the comparative study of colistin and TOBI® [9], where marked improvements in lung function were shown in patients harbouring organisms with high minimum inhibitory concentration to tobramycin. This has been reproduced

in studies of inhaled aztreonam [10, 11], adding further weight to the argument that *in vitro* measures of resistance are not appropriate to determine antibiotic choice for aerosolised therapy.

Since the publication of the Ramsey study [7] the regulatory agencies have correctly regarded TOBI® as a gold standard therapy. Thus, completion of a comparative study of TOBI® *versus* aztreonam lysine over 6 months (three 28-day cycles, month on/month off) has been a requirement for registration of inhaled aztreonam lysine in Europe [12]. Whilst this is useful for establishing equivalence of a month on/month off regimen of one or other preparation it does not inform us of the best regimen for treating chronic *P. aeruginosa* infection in CF. There is a requirement to find the regimen that delivers the best clinical outcomes with the least development of long-term resistance. Proponents of the month on/month off regimen suggest this preserves susceptibility of the organisms and indeed detailed examination of susceptibility testing of *P. aeruginosa* isolates during trials of month on/month off aztreonam lysine supports that view [13], but many CF patients with chronic *P. aeruginosa* infection do not like a month of no nebulised antibiotic with an associated fall in lung function. Thus, clinicians have adopted an alternating month approach of TOBI®/colomycin or aztreonam lysine (Cayston®; Gilead, Foster City, CA, USA)/TOBI®. There are no trials to guide this practice and evaluation of these alternative approaches is required. In the meantime, current guidelines state that patients with chronic infection with *P. aeruginosa* benefit from aerosolised anti-pseudomonal therapy both in terms of lung function and reduction in number of exacerbations [14]. Debate about the choice of agent, single or combination therapy, and continuous or intermittent dosing will remain until further post-marketing collaborative trials are performed.

As nebulised antibiotic therapy has become established therapy in CF, the patients have demanded that we look at easing the treatment burden. As a result dry powder antibiotic preparations have been explored to avoid the need for time consuming procedures such as cleaning and sterilising of nebulisers and equipment.

Dry powder tobramycin has been licenced in CF on the basis of equivalence studies to nebulised TOBI® [15]. In addition, dry powder colomycin has also been approved by the European Medicines Agency.

CF patients now have multiple options for chronic treatment of chronic *P. aeruginosa* infection but it should be emphasised that early eradication therapy *via* the inhalational route has become standard of care to delay and/or prevent chronic bronchial infection with *P. aeruginosa*. The study by Ratjen *et al.* [16] will now provide the gold standard of early treatment studies. The comparison of two alternate regimens of TOBI® (28 and 56 days of tobramycin inhalation solution 300 mg/5 mL twice daily) in a well-controlled randomised study leaves us with a clear message that eradication can be achieved with a single cycle of TOBI® and that this is likely to become the gold standard for future comparative studies.

In the USA, TOBI® is recommended [14] as nebulised colistin is not licensed by the Food and Drug Administration (FDA), but in Europe, colistin (in combination with oral ciprofloxacin) has been recommended for first-line use for eradication [17]. However, the duration of therapy is not standardised and ranges from 3 to 4 weeks to 6 to 12 months. Whilst nebulised antibiotics may sometimes be utilised in treatment of exacerbations there are no specific studies to guide this practice.

Inhaled antibiotics in non-CF bronchiectasis

Although there have been studies of nebulised amoxicillin in bronchiectasis for the treatment of patients with *H. influenzae* infection [18] the majority of recent studies focus on treatment of *P. aeruginosa* infection. TOBI® (tobramycin for inhalation 300 mg) was evaluated carefully in non-CF bronchiectasis in the study by Barker *et al.* [19] and demonstrated impressive microbial efficacy in a 4-week randomised placebo controlled study of TOBI® with a 4.5 $\log_{10}$ CFU per mL reduction in *P. aeruginosa* density compared to placebo (twice the level of $\log_{10}$ CFU per mL reduction seen in CF). However, more patients in the active group experienced adverse events compared to placebo, a phenomenon that had not been seen in CF studies. The theme of increased

side-effects despite microbial efficacy was seen in an open label study of the same product in which 20% of patients withdrew because of treatment-related side-effects whilst those who did not experienced significant improvements in quality of life and pulmonary symptom scores [20]. A careful evaluation of this product in bronchiectasis with lower doses to explore a dose that retains microbiological effectiveness but removes the treatment related side-effects is still awaited. DROBNIC *et al.* [21] studied an alternative preparation of the same dose of tobramycin in a double-blind placebo-controlled cross-over trial in 30 patients and found a significant microbial efficacy signal but no difference in number of exacerbations, lung function or quality of life. Thus, despite an antimicrobial effect clinical efficacy for tobramycin at a dose of 300 mg has been lacking.

More recently, MURRAY *et al.* [22] published a 12-month randomised trial of gentamycin 80 mg twice daily *versus* 0.9% saline in 65 patients with bronchiectasis. This study was not confined to patients with *P. aeruginosa*. This is a significant study in that it demonstrated both a reduction in bacterial density and a reduction in exacerbations, thus, giving proof of concept to the hypothesis that a chronic inhaled suppressive therapy in non-CF bronchiectasis that reduces bacterial density will also reduce exacerbations. Also of note is the fact that almost one-third of the patients with *P. aeruginosa* at the start had eradicated the organism in response to therapy. Importantly no gentamicin resistant isolates of *P. aeruginosa* developed. This study is common with others in that bronchiectasis showed no change in lung function.

Future studies in non-CF bronchiectasis should benefit from the insights we have gained over the past few years. Namely that similar doses to those used in CF may show superior microbial efficacy but side-effects may be different so that appropriate dose ranging studies to find the best tolerated dose with maximal effect are required. In addition, after successful proof of concept studies over 4 weeks, longer term studies should focus on clinical efficacy based on a reduction in exacerbations. Lung function is of course important as a safety measure to monitor occurrence of treatment-related bronchospasm but it does not form a good primary end-point to assess efficacy of inhaled antibiotics in non-CF bronchiectasis.

The study by MURRAY *et al.* [22] further opens the discussion as to whether inhaled antibiotic therapy should be reserved for patients infected with *P. aeruginosa* or whether they should be used in a more widespread way.

It is likely that patients whose quality of life is impaired by frequent exacerbations and persistent symptoms will take on the burden of twice daily nebulised therapy more readily than those who have infrequent exacerbations. Thus, many of us have limited our studies of nebulised therapies to patients with *P. aeruginosa* infection. The recent development of dry powder antibiotic preparations that can be administered by a portable inhaler device has broadened our thinking and we now have a study of dry powder inhaled ciprofloxacin in non-CF bronchiectasis not limited to those with *P. aeruginosa* infection [23].

In a proof-of-concept study [23], adults who were culture positive for pre-defined potential respiratory pathogens (including both *P. aeruginosa* and *H. influenzae*) were randomised to ciprofloxacin dry powder for inhalation (DPI) 32.5 mg or placebo administered twice daily for 28 days.

60 subjects received ciprofloxacin DPI 32.5 mg and 64 received placebo. Subjects on ciprofloxacin DPI had a significant reduction ($p<0.001$) in sputum total bacterial load at the end of treatment (-3.62 $\log_{10}$ CFU per mL) compared with placebo. In the ciprofloxacin DPI group, 35% of subjects reported pathogen eradication at the end of treatment *versus* 8% in the placebo group. No abnormal safety results were reported and rates of bronchospasm were low. Thus, the scene is set for a large study to look at exacerbations in a similar population.

It is encouraging that there is currently so much interest in treating chronic bronchial infection in non-CF bronchiectasis and that there are several studies on-going or just reporting either nebulised or dry powder antibiotics; these are summarised in table 1. Liposomal amikacin has the advantage of being a once daily preparation with the aminoglycoside amikacin being packaged in a liposome. Results of phase II trials in non-CF bronchiectasis are promising [24] and trials of this

Table 1. New formulations of inhaled antibiotics in non-cystic fibrosis bronchiectasis

Therapy	Phase	Subjects n	Description	Result
Liposomal amikacin for inhalation [24]	II	61	Inhaled liposomal amikacin 280 mg or 560 mg once daily for 28 days	Significant decrease in *P. aeruginosa* density in the 560 mg arm *versus* placebo
Aztreonam for inhalation solution [25]	II	89	Nebulised aztreonam for inhalation solution 75 mg three times daily for 28 days	Statistically and clinically significant improvement in respiratory symptoms Significant decrease of *P. aeruginosa* (>99%) and non- *P. aeruginosa* (98%) Gram-negative density
Dual release ciprofloxacin for inhalation ARD-3150 [26]	IIb	42	ARD-3150 and placebo once daily for 28 days followed by 28 days off treatment for three cycles	Significant decrease of *P. aeruginosa* density in per protocol population 4.2 $\log_{10}$ CFU per mL *versus* 0.1 $\log_{10}$ CFU per mL placebo (p=0.004) Significant difference in median time to first exacerbation (dual release ciprofloxacin for inhalation) 134 days *versus* placebo 56 days (p=0.046)
Ciprofloxacin DPI [23]	II	124	Ciprofloxacin DPI 32.5 mg or placebo twice daily for 28 days plus 2 months' follow-up	Significant decrease of total bacterial counts in intention-to-treat population 3.6 $\log_{10}$ CFU per mL *versus* 0.3 $\log_{10}$ CFU per mL placebo (p=0.001)

DPI: dry powder for inhalation; *P. aeruginosa*: *Pseudomonas aeruginosa*.

agent are on-going in CF and in non-tuberculous mycobacterial lung infection. Aztreonam lysine is already licenced in CF and is a three times daily nebulised therapy with antimicrobial efficacy seen in non-CF bronchiectasis [25]. Finally, a nebulised preparation of ciprofloxacin which benefits from a mixture of free ciprofloxacin coupled with ciprofloxacin packaged in liposomes has undergone studies looking at time to next exacerbation [26]. We eagerly await full publication of these studies and phase III trials to help plan the way ahead for inhaled antibiotics in non-CF bronchiectasis. The questions are slightly different from those in CF in that the goal will be to reduce exacerbations rather than change lung function and the regimen may well be different. The data suggests that in bronchiectasis, despite apparent chronic infection with *P. aeruginosa*, eradication on inhaled regimens is possible. Hence, whereas treatment for chronic infection in CF is deemed lifelong, a much more flexible approach may apply to non-CF bronchiectasis. In both disorders, however, efforts must be made to find a regimen that reduces risk of long-term resistance.

Finally, it is inevitable that considerations will be given to patients with chronic obstructive pulmonary disease (COPD) who have recurrent infections with difficult Gram-negative organisms and whose exacerbations are often associated with hospital admission. This group will require careful thought and study. A phase II study of inhaled levofloxacin has been completed with COPD patients receiving twice daily active or placebo nebulised therapy for 5 days out of each month for 12 months [27]. The study failed to show a reduction in exacerbations. It is clear that we do not yet understand the optimal regimen for therapy in COPD. Lessons have been learnt in terms of not applying the same dose or regimen from CF in non-CF bronchiectasis. Furthermore, the side-effect profile may be different. It is crucial that dose ranging tolerability studies are performed followed by appropriate trials to ensure the safety and efficacy of the inhaled route in this population.

Conclusions

Inhaled antibiotics represent an effective therapy for eradication and chronic suppression of *P. aeruginosa* in CF resulting in improved lung function and reduced exacerbations. Data are emerging that suggests a similar approach in non-CF bronchiectasis will reduce bacterial burden and lead to reduced exacerbations. In the next few years it is likely that several new options will emerge and it is our challenge to find the optimal regimens that will keep patients stable and limit the development of antibiotic resistance.

Statement of Interest

D. Bilton has received fees for expert consultancy on trial design with Novartis and advisory board attendances for Bayer, Insmed, Novartis and Gilead.

References

1. Heijerman H, Westerman E, Conway S, *et al.* Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2009; 8: 295–315.
2. Falagas ME, Michalopoulos A, Metaxas EI. Pulmonary drug delivery systems for antimicrobial agents: facts and myths. *Int J Antimicrob Agents* 2010; 35: 101–106.
3. Michalopoulos A, Papadakis E. Inhaled anti-infective agents: emphasis on colistin. *Infection* 2010; 38: 81–88.
4. Jensen T, Pedersen SS, Garne S, *et al.* Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. *J Antimicrob Chemother* 1987; 19: 831–883.
5. Hodson ME, Penketh AR, Batten JC. Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. *Lancet* 1981; 2: 1137–1139.
6. Mukhopadhyay S, Singh M, Cater JI, *et al.* Nebulised antipseudomonal antibiotic therapy in cystic fibrosis: a meta-analysis of benefits and risks. *Thorax* 1996; 51: 364–368.
7. Ramsey BW, Pepe MS, Quan JM, *et al.* Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999; 340: 23–30.
8. Ramsey BW, Dorkin HL, Eisenberg JD, *et al.* Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med* 1993; 328: 1740–1746.
9. Hodson ME, Gallagher CG, Govan JR. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. *Eur Respir J* 2002; 20: 658–664.
10. Retsch-Bogart GZ, Quittner AL, Gibson RL, *et al.* Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest* 2009; 135: 1223–1232.
11. McCoy KS, Quittner AL, Oermann CM, *et al.* Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Respir Crit Care Med* 2008; 178: 921–928.
12. Assael BM, Pressler T, Bilton D, *et al.* Inhaled aztreonam lysine *vs.* inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. *J Cyst Fibros* 2013; 13: 130–140.
13. Oermann CM, McCoy KS, Retsch-Bogart GZ, *et al. Pseudomonas aeruginosa* antibiotic susceptibility during long-term use of aztreonam for inhalation solution (AZLI). *J Antimicrob Chemother* 2011; 66: 2398–2404.
14. Flume PA, O'Sullivan BP, Robinson KA, *et al.* Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007; 176: 957–969.
15. Konstan MW, Flume PA, Kappler M, *et al.* Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: the EAGER trial. *J Cyst Fibros* 2011; 10: 54–61.
16. Ratjen F, Munck A, Kho P, *et al.* Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax* 2010; 65: 286–291.
17. Doring G, Conway SP, Heijerman HG, *et al.* Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: a European consensus. *Eur Respir J* 2000; 16: 749–767.
18. Stockley RA, Hill SL, Burnett D. Nebulised amoxicillin in chronic purulent bronchiectasis. *Clin Ther* 1985; 7: 593–599.
19. Barker AF, Couch L, Fiel SB, *et al.* Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *Am J Respir Crit Crae Med* 2000; 162: 481–485.
20. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest* 2005; 127: 1420–1426.
21. Drobnic ME, Sune P, Montoro JB, *et al.* Inhaled tobramycin in non cystic fibrosis bronchiectsis and chronic bronchial infection with *Pseudomonas aeruginosa. Ann Pharmacother* 2005; 39: 39–44.
22. Murray MP, Govan JR, Doherty CJ, *et al.* A randomised controlled trial of nebulised gentamycin in non cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2011; 183: 491–499.
23. Wilson R, Welte T, Polverino E, *et al.* Ciprofloxacin DPI in non-cystic fibrosis bronchiectasis: a phase II randomised study. *Eur Respir J* 2013; 41: 1107–1115.

24. O'Donnell A, Swarnakar R, Yashina L, *et al.* A placebo controlled study of liposomal amikacin for inhalation once daily in the treatment of bronchiectasis patients with chronic *Pseudomonas aeruginosa* lung infection. *Eur Respir J* 2009; 34: Suppl. 53, 231s.
25. Barker A, O'Donnell A, Daley C, *et al.* Microbiological results of a phase 2 open label study of aztreonam for inhalation in patients with bronchiectasis and gram negative bacteria in the airways. *Chest* 2010; 138: 512A.
26. Serisier DJ, Bowler SD, McGuckin M, *et al.* The bronchiectasis and low dose erythromycin study (BLESS). *Am J Respir Crit Care Med* 2012; 185: A6862.
27. Sethi S, Rennard SI, Miravitiles M, *et al.* A phase 2 study to evaluate the safety, tolerability and efficacy of Levofloxacin inhalation solution (mp-376) administered for 5 days every 28 days to prevent acute exacerbations in high risk COPD patients. *Am J respir Crit Care Med* 2012; 185: A3037.

Chapter 13

Prevention and treatment of exacerbations of non-CF bronchiectasis

Jessica Rademacher and Felix C. Ringshausen

SUMMARY: This chapter focuses on the prevention and treatment of exacerbations of non-cystic fibrosis (CF) bronchiectasis among adults. Due to a paucity of interventional randomised controlled trials the prevention and treatment of exacerbations is mostly empirical. However, patient education, physiotherapy and pharmacological airway clearance are the cornerstones of chronic management. In subjects with frequent exacerbations and chronic Gram-negative bacterial colonisations, inhaled antibiotics or anti-inflammatory macrolide long-term therapy should be considered, with the aim being to keep the number of exacerbations as low as possible. In acute exacerbations, empirical antibiotic therapy should be guided by the findings of previous sputum cultures, local epidemiology and patient factors, such as disease severity and (long-term) antibiotic pre-treatment, which determine the risk of infection by *Pseudomonas aeruginosa* or other difficult-to-treat or multidrug-resistant organisms. The majority of recommendations given in this chapter are based on comparatively small studies or expert opinions. Well-designed, randomised controlled trials in this field of respiratory medicine are urgently needed.

KEYWORDS: Antibiotics, bronchiectasis, exacerbation, prevention, prophylaxis, treatment

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Eur Respir Monogr 2013; 60: 127–136.
Copyright ERS 2013.
DOI: 10.1183/1025448x.10018212
Print ISBN: 978-1-84984-034-7
Online ISBN: 978-1-84984-035-4
Print ISSN: 1025-448x
Online ISSN: 2075-6674

The term bronchiectasis describes a permanent dilatation of the bronchi and bronchioles as a result of the destruction of their smooth muscles and elastic connective tissues. Commonly, the disorder starts with the narrowing of airways, which may be triggered by an infection and lead to the destruction of the epithelium. The subsequent dysfunction of the mucociliary clearance results in the retention of secretions and predisposes the patient for repeated airway infections in terms of a vicious circle [1]. The treatment aims in stable bronchiectasis patients are to control symptoms, enhance the health-related quality of life (QoL), reduce the frequency of exacerbations

and preserve lung function. While there is clear evidence that patients with frequent exacerbations of bronchiectasis have worse QoL and more severe disease [2], the notion that exacerbations promote the accelerated decline of lung function and increase mortality is mostly derived from observations of patients with chronic obstructive pulmonary disease (COPD) [3]. Nevertheless, the reduction of exacerbations is probably the primary goal of future research in bronchiectasis [4]. In a recent study, bacterial colonisation status was associated with mortality, exacerbation frequency, symptoms and reduced lung function [5].

The use of antibiotics in patients with bronchiectasis can be divided into the preventions of exacerbations, their treatment and the eradication of chronically colonising organisms.

Prevention of exacerbations of non-cystic fibrosis bronchiectasis

Physiotherapy and pharmacological airway clearance

Respiratory physiotherapy is the basic treatment for bronchiectasis in order to improve the drainage of secretions, deal with dyspnoea and prevent exacerbations. All patients with bronchiectasis who have chronic productive cough and/or evidence of mucus plugging on high-resolution computed tomography (HRCT) of the chest should be taught airway clearance techniques by a dedicated chest physiotherapist [4]. The aims of respiratory physiotherapy include: the mobilisation and improved expectoration of airway secretions; the enhanced efficacy of ventilation; the preservation or, at best, the augmentation of exercise tolerance; and improved disease knowledge and understanding, as well as the reduction of breathlessness and thoracic pain [6]. The mainstay of treatment is sufficient oral fluid intake for secretolytic purposes. This can be supported by the inhalation of hypertonic saline, which has been found to be beneficial in stable patients [7]. The raised salt concentration in the nebulised solution results in the osmotic penetration of fluid into the secretions, thus improving their rheological properties, which, in turn, results in faster and more efficient airway clearance.

In a recent, randomised controlled trial by NICOLSON *et al.* [8], the effect of inhaled hypertonic saline (6%) was tested *versus* isotonic saline (0.9%) in 40 non-cystic fibrosis (CF) bronchiectasis patients. Treatment over 12 months was well tolerated and resulted in similar, clinically important benefits with significant improvements seen in QoL, lung function and sputum colonisation in both groups. There were no differences in exacerbation rates between groups. This study demonstrates that the long-term inhalation of a saline solution in patients with non-CF bronchiectasis is a safe and potentially beneficial treatment. The effect on exacerbation rate needs to be examined in a larger study. Therefore, the choice of the inhaled saline therapy (isotonic or hypertonic) may be guided by the individual patient's tolerance and preference [8]. The duration and the frequency of the airway clearance exercises should be at least 20–30 mins once or twice a day [4].

In contrast to other hyperosmolar solutions, mannitol has the hypothetical advantage of a longer half-life within the airways. A disadvantage of mannitol is that the airway hyperresponsiveness increases during inhalation. In an open-labelled, non-controlled study over 12 days the QoL, lung function and sputum viscosity were notably improved by mannitol [9]. Some other smaller studies, which investigated mannitol, also showed a very promising treatment effect for patients with stable non-CF bronchiectasis [10]. However, the evidence for recommending the use of mannitol in the treatment of patients with non-CF bronchiectasis is actually weak [11]. Adequately powered randomised and controlled trials are required to assess the efficacy of this drug in a wider perspective, looking at both immediate and long-term effects.

Other interventions for stable bronchiectasis, for which clear evidence is currently lacking but which may be beneficial to patients on an individual basis, include specific physical inspiratory muscle training and pulmonary rehabilitation [12, 13], positive expiratory pressure and high-frequency oscillation therapy [14, 15], as well as mucolytics [16].

Vaccinations

No randomised studies of vaccinations exist for this group of patients. The effect of annual influenza vaccination has been proved for other chronic airway diseases, such as COPD, and translates to patients with bronchiectasis. Data from a single study have shown that the 23-valent pneumococcal vaccine, given in addition to the seasonal influenza vaccination, may be beneficial, although a final conclusion cannot be drawn currently [17]. In principle, it is recommended that healthcare providers adhere to national vaccination guidelines [18].

Anti-inflammatory therapies

In analogy with acute exacerbations of COPD (AECOPD), oral corticosteroids are often administered when acute exacerbations of bronchiectasis occur. However, there is no evidence for a role of oral corticosteroids in stable bronchiectasis [19]. For inhaled steroids, long-term usage seems to confer small benefits. In a study of 86 patients with non-CF bronchiectasis by TSANG *et al.* [20], no change in exacerbation frequency or lung function was found. However, sputum volume was improved when steroids were inhaled, and patients with *Pseudomonas aeruginosa* infections gained a particular benefit [20]. Overall, randomised controlled studies are limited and do not support the routine use of inhaled corticosteroids in bronchiectasis, although an individual therapeutic trial may be justified [4, 21, 22].

Macrolide antibiotics, such as azithromycin, have a potent anti-inflammatory effect in addition to their antibacterial properties. They reduce the production of pro-inflammatory cytokines, which attract neutrophils and promote the expression of essential adhesion molecules for their migration from the bloodstream to the lung interstitium. In addition to, and independently of, their regular bacteriostatic effects, macrolides inhibit the production of biofilms by *P. aeruginosa* [23].

In a recent study, treatment with macrolides led to a reduction in the amount of sputum and improved 5-year survival rate in patients with non-CF bronchiectasis [24]. Recently, WONG *et al.* [25] confirmed the benefit of azithromycin and demonstrated a significant decline in the rate of event-based exacerbations and an increased time to the next exacerbation compared to placebo in a study of 141 patients with bronchiectasis. However, patients with mild disease should not be treated with long-term azithromycin unless there is major morbidity or evidence of disease progression despite adherence to physiotherapy and the early use of broad-spectrum antibiotics for infective exacerbations [26].

Long-term antibiotic prophylaxis

The importance of antibiotic treatment outside exacerbations is the subject of controversy. To date, attempts to reduce the amount of pathogens by means of long-term oral antibiotic treatment and to lower the rate of exacerbations have remained unsuccessful. The emergence of antimicrobial resistance in patients receiving long-term antibiotic therapy may be important in this context. A systematic review of randomised controlled trials, which included the use of macrolides as well as nebulised antibiotics, reported no benefit of prolonged antibiotic use in bronchiectasis in terms of reducing exacerbations (nine trials overall, including 378 patients; OR 0.96, 95% CI 0.27–3.46) [27]. The authors could find no evidence on benefits regarding markers of airway inflammation. In a study by TSANG *et al.* [28], bronchiectasis patients were randomised in a double-blind placebo-controlled manner to either low-dose erythromycin or placebo. However, no treatment benefits on airway inflammatory markers, including interleukin (IL)-1α, IL-8, tumour necrosis factor (TNF)-α and leukotriene B_4, were found. Conversely, HILL *et al.* [29] showed reduced elastase activity in sputum after treatment with amoxicillin. In a large recent study by CHALMERS *et al.* [30], a direct relationship between bacterial load as well as airway and systemic inflammation was demonstrated among 385 stable bronchiectasis patients. Over 1 year, patients with high bacterial loads had a higher frequency of exacerbations and were more likely to require hospitalisation due to severe exacerbations. This relationship was independent of severity of bronchiectasis as assessed by computed tomography (CT) scanning and spirometry. Moreover,

higher bacterial loads were associated with more severe respiratory symptoms as assessed by the St George Respiratory Questionnaire (SGRQ) and more severe cough as assessed by the Leicester Cough Questionnaire.

Elective intravenous antibiotics in adults with bronchiectasis

A significant proportion of patients with very severe bronchiectasis have recurrent exacerbations and quickly relapse on cessation of antibiotics. In addition, these patients are more often colonised with *P. aeruginosa*, enteric Gram-negative organisms and methicillin-resistant *Staphylococcus aureus* (MRSA) [31, 32]. In CF, elective and timed *i.v.* antibiotics are used in clinical practice in patients with chronic *P. aeruginosa* colonisation. There is evidence to suggest that increased survival probability may coincide with the elective application of *i.v.* antibiotics [33]. One single study has been carried out in non-CF bronchiectasis. In a very recent study by MANDAL *et al.* [34], the treatment with 8-weekly *i.v.* antibiotics in severe bronchiectasis reduced the exacerbation frequency and improved the exercise tolerance and the health-related QoL. The impact of a 14-day antibiotic therapy on markers of airway inflammation and systemic inflammation, as well as exacerbations, was investigated in a study by CHALMERS *et al.* [30]. Among stable patients, 15 subjects were treated with *i.v.* antibiotics for a period of 14 days, while 11 subjects received no therapy. Sputum and serum markers, as well as quantitative sputum culture results, were compared between these two groups. After 14 days of *i.v.* antibiotic treatment, all treated patients had no significant bacterial growth in sputum. In contrast, in the control group that received no antibiotic therapy, there was no reduction in the bacterial load. Future intervention studies are necessary to answer the question of timed *i.v.* antibiotics to reduce the frequency of exacerbations in patients with stable bronchiectasis.

Nebulised antibiotic prophylaxis

Inhaled antibiotics are a standard treatment regimen for patients with CF who are colonised with *P. aeruginosa* [35]. Since up to 25% of patients with non-CF bronchiectasis are colonised with *P. aeruginosa*, this therapeutic approach may also offer an advantage in this setting. So far, some smaller studies have demonstrated the importance of inhaled antibiotics in non-CF bronchiectasis. Significant clinical improvement, along with a reduced density of pathogens and the eradication of *P. aeruginosa,* was shown in up to 35% of subjects [36]. Patients receiving treatment with inhaled tobramycin had fewer symptoms and an improved QoL [37]. Inhaled colistin led to improvements in lung function and QoL [38]. Furthermore, a reduction in hospital admissions and exacerbations has been reported [39]. Inhaled aztreonam lowered the rate of exacerbations, reduced symptoms and improved lung function in patients with CF [40]. A study of inhaled aztreonam in non-CF bronchiectasis subjects is currently being performed and recruitment has recently been (clinicaltrial.gov identifier number of inhaled aztreonam: NCT01314716). A dry powder formulation of inhaled ciprofloxacin reduced the bacterial load of *P. aeruginosa* in a recent phase II trial [41]. Further studies of inhaled amikacin and intratracheal instillation of fosfomycin/tobramycin are expected. In a recent randomised controlled study, inhaled gentamycin led to the eradication of *P. aeruginosa* in 31% of cases and postponed the interval to the next exacerbation (120 days *versus* 62 days) [42]. Another study of inhaled gentamycin found a decreased rate of exacerbations and an improved QoL [43]. CHALMERS *et al.* [30] demonstrated that nebulised gentamicin resulted in a significant reduction of sputum IL-8, TNF-α and IL-1β compared to patients treated with normal saline. For the soluble adhesion molecules, reductions were evident for intercellular adhesion molecule (ICAM)-1 compared with baseline and the saline-treated group at 12 months. E-selectin was significantly different from baseline in the gentamicin group, but did not differ compared to the saline group.

Patients with three or more exacerbations per year requiring antibiotic therapy, patients with fewer exacerbations that are causing significant morbidity or those with chronic colonisation by *P. aeruginosa* should be considered for long-term nebulised antibiotics.

Eradication therapy

Chronic infection with *P. aeruginosa* commonly occurs as the disease progresses and lung function worsens. It is associated with increased symptoms [44], decreased QoL [2] and potentially promotes the further accelerated decline of lung function [45, 46]. Treatment of exacerbations among patients infected with *Pseudomonas* often requires hospital admission for *i.v.* antibiotics due to the fact that the organism is frequently resistant to oral antibiotics [47]. In patients with CF, early treatment of *Pseudomonas* following its first cultural detection is well established and reduces the risk of chronic colonisation, which in this population is associated with poorer outcomes [48]. Based on this, it could be postulated that early and aggressive treatment in non-CF bronchiectasis may also improve outcomes. The British Thoracic Society (BTS) guideline recommends an attempt to eradicate *P. aeruginosa* early [4]. Initially, high doses of oral ciprofloxacin and, as second-line treatment, further oral, *i.v.* and/or nebulised anti-pseudomonal antibiotics are used (fig. 1) [4]. However, there are no prospective studies in non-CF bronchiectasis assessing eradication therapy among recently infected patients. The retrospective study by WHITE *et al.* [48] assessed clinical and microbiological outcomes after eradication therapy following *Pseudomonas* infections and showed a significant reduction of exacerbation frequency and an eradication rate of 80%. However, 11 (46%) out of 24 subjects were subsequently re-infected after a median time of 6 months. Nevertheless, these findings may indicate that the eradication of *Pseudomonas* can be achieved in a high proportion of patients, which may lead to prolonged clearance and reduced exacerbation rates. However, these results require confirmation in a prospective study.

Other treatment options and future perspectives

Additional individual treatment options with a lack of evidence for efficacy or safety include anticholinergics [49], long-acting β_2-agonists [50], leukotriene receptor antagonists [51], oral methylxanthines [52], inhaled nonsteroidal anti-inflammatory drugs [53] and surgical interventions [54]. However, usually bronchodilators are prescribed according to the extent of the obstructive airflow limitation [4]. A single study found no benefit of specialist nurse practitioner care over conventional care in the outpatient setting [55]. Another, interesting approach, currently only supported by a single recent study, may be to search for and treat vitamin-D deficiency, which was found to be associated with disease severity and chronic bacterial colonisation [56].

Treatment of exacerbations of non-CF bronchiectasis

In spite of the wide usage of the term exacerbation, there is no standardised definition in the paediatric or the adult medical literature and actually little data on associated clinical features. As symptoms of bronchiectasis share characteristics and often coexist with COPD [57, 58], the definition of exacerbation in COPD in adults by ANTHONISEN *et al.* [59] has been applied to bronchiectasis studies to a variable extent. Due to the absence of a validated definition even less is known about the clinical features associated with

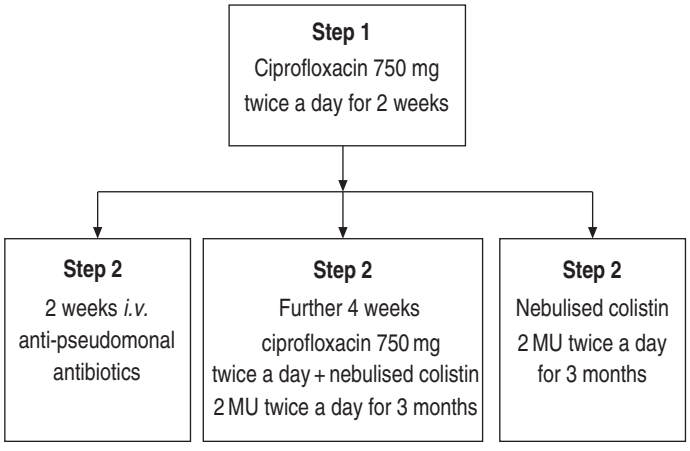

Figure 1. Eradication algorithm for *Pseudomonas aeruginosa* in adults. Attempt to eradicate with a 2-week course of oral ciprofloxacin (step 1). If step 1 fails, further regimes must be considered (step 2). Reproduced from [4] with permission from the publisher.

treatment success or failure with oral or *i.v.* antibiotics and influence of viral respiratory illnesses, as well as changes in lung function and sputum microbiology during an exacerbation. A standardised definition and an understanding of features associated with exacerbations is not only important for clinicians, especially non-respiratory physicians who care for patients with non-CF bronchiectasis, but also for future research studies. KAPUR *et al.* [60] found an increase in the cough frequency and a change in its character to be the most common of the symptoms associated with an exacerbation in 88% and 67% of patients, respectively. Increased sputum volume, purulence and fever were other common features of exacerbations in 42%, 35% and 28% of subjects, respectively, while chest pain, dyspnoea, haemoptysis and tachypnoea were rare. 56% of subjects had a worsening in their chest auscultation findings during an exacerbation. Spirometry was not significantly different between the stable and the exacerbation state. In the first instance, patients with an infective exacerbation of bronchiectasis should be assessed for the need of inpatient or outpatient treatment. In the study by KAPUR *et al.* [60], 35% of exacerbations failed to respond to an oral antibiotic regimen and required subsequent hospital admission. Prophylactic antibiotic therapy was the only significant predictor of failure of oral therapy with an adjusted OR of 6.77 (95% CI 2.06–19.90; p=0.003). As the treatment of exacerbations should be initiated as early as possible, it is important that bronchiectasis patients understand the basic principles of disease management and are able to recognise an exacerbation as such.

FINKLEA *et al.* [61] evaluated the factors associated with mortality in hospitalised patients with an acute exacerbation of bronchiectasis. Male sex, elevated creatinine levels, decreased forced expiratory volume in 1 s (FEV_1) (% predicted), mechanical ventilation, history of smoking and the use of systemic steroids during the current hospitalisation were associated with an increased risk of mortality [61]. Table 1 gives an overview of the recommended assessment in patients with exacerbations.

Oral antibiotic treatment

In an acute exacerbation of bronchiectasis, antibiotics should be administered if an increase in dyspnoea and sputum volume is observed and the sputum colour has changed to a yellow–green or greenish tinge. Before starting antibiotics a sputum sample should be sent off for culture. To date, there are no randomised controlled trials for the use of antibiotics in exacerbations of bronchiectasis.

If a patient is known to have chronic colonisation with respiratory pathogens, targeted treatment should be initiated in consideration of the latest antibiogram. If no prior microbiological result is available a broad-spectrum antibiotic should be selected for the initial treatment, taking the local epidemiology into account. Usually, this empiric treatment should include coverage of *Pseudomonas* strains, since these pathogens are to be expected particularly among severely ill patients or patients with advanced disease and may determine the patient's prognosis. However, the microbiology of bronchiectasis may vary, depending on the local epidemiology, the healthcare setting and disease severity. For example, while the BTS guideline recommends amoxicillin as the first-line treatment of choice in subjects without previous bacteriology, due to the fact that *Haemophilus influenzae* is considered to be the most prevalent organism isolated

Table 1. Assessment of patients with exacerbations of bronchiectasis

Outpatients
History
Clinical examination
Sputum for culture (if possible prior to commencement of antibiotics)
Review of previous sputum microbiology
Inpatients
History
Clinical examination
Oxygen saturation on air
Arterial blood gases if indicated
ECG if indicated
Chest radiograph
Sputum for culture (if possible prior to commencement of antibiotics)
Blood culture if pyrexial >38°C
Full blood count, urea, electrolytes and liver function tests
C-reactive protein
Review of previous sputum microbiology
If feasible, 24 h sputum weight or volume

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[4], German guidelines on adult lower respiratory tract infections recommends empirical coverage for *P. aeruginosa* in every subject with known bronchiectasis [62].

In the outpatient setting, the oral fluoroquinolones levofloxacin or ciprofloxacin are the only available options. However, it needs to be borne in mind that ciprofloxacin may not be sufficiently effective against *Streptococcus pneumoniae*, the most common bacterial pathogen in community-acquired pneumonia and acute lower respiratory tract infections. PLETZ *et al.* [63] reported the case of a patient with bronchiectasis, in whom consecutive courses of treatment failed in the presence of a ciprofloxacin-resistant pneumococcal strain. The optimal duration of antibiotic therapy is unknown and requires further study. However, it is expert consensus that an antimicrobial treatment course of 14 days should be applied to all exacerbations of bronchiectasis [4].

Intravenous antibiotic treatment

In inpatients, the scope of antimicrobial drugs with efficacy against *P. aeruginosa* is wider (*e.g.* carbapenems, cephalosporins with anti-pseudomonal activity, and ureidopenicillins). Whether combination therapy, using a β-lactam antibiotic together with an aminoglycoside or a fluoroquinolone, is superior to monotherapy with a drug that is active against *Pseudomonas* is subject to debate. The BTS guidelines do not recommend combination therapy in patients colonised with *H. influenzae, Moraxella catarrhalis, S. aureus* (methicillin-sensitive) and *S. pneumoniae*. Combination therapy should be used for infections due to strains of *P. aeruginosa* that are resistant to one or more anti-pseudomonal antibiotic [4]. In hospitalised patients who are not at risk for *P. aeruginosa* treatment with an aminopenicillin/β-lactamase inhibitor or a third-generation cephalosporin is recommended. An attempt to diagnose the pathogen should be made before antibiotics are initiated and the antibiotic treatment should be tailored according to the results of the subsequent sputum culture.

Nebulised antibiotic treatment

Previous studies in chronic purulent bronchitis have suggested that the combination of *i.v.* and inhaled antibiotics may have greater efficacy than *i.v.* therapy alone [64, 65]. BILTON *et al.* [66] added inhaled tobramycin to oral ciprofloxacin for the treatment of acute exacerbations due to the presence of *P. aeruginosa* in bronchiectasis and showed an improved microbiological outcome, which was concordant with the clinical outcome [66]. Further well-designed studies are needed to answer the efficacy of a combined systemic and nebulised treatment strategy.

Noninvasive ventilation

While noninvasive ventilation (NIV) is an accepted and widely used treatment option for acute- and chronic-hypercapnic respiratory failure due to a variety of underlying pathologies, specific data on bronchiectasis is virtually unavailable [67]. However, NIV is increasingly used in CF patients besides bridge-to-transplant strategies and may possibly gain more scientific interest in advanced non-CF bronchiectasis patients in the near future [68–71].

Conclusion

In summary, the prevention or the reduction of exacerbations should be the preferential aim of the management of stable bronchiectasis patients. The basic treatments are physiotherapy and mucolytic or hyperosmolar therapies for sufficient airway clearance. In cases of frequent exacerbations and Gram-negative colonisation, treatment with inhaled antibiotics or macrolide long-term therapy should be considered. In an acute exacerbation the findings of previous sputum cultures, the local epidemiology and patient factors, such as disease severity and (long-term) antibiotic pre-treatment, should be considered when choosing the empirical antibiotic therapy. However the management of exacerbations in bronchiectasis is largely empirical, due to the paucity of high-quality clinical trials. The majority of recommendations given in this chapter are

based on comparatively small studies or expert opinions. Adequately powered, randomised controlled trials in this field of respiratory medicine are urgently needed. Due to the paucity of evidence-based data and the lack of approved therapies for non-CF bronchiectasis, treatment options are extraordinarily limited, in particular in private practice and outpatient care. National or, preferably, international patient registries could help to better understand the prognostic factors and the optimal treatment options for non-CF bronchiectasis.

Statement of Interest

None declared.

References

1. Wilson R. A vicious circle hypothesis operating during infective exacerbations of chronic bronchitis. *Monaldi Arch Chest Dis* 1994; 49: 159–164.
2. Wilson CB, Jones PW, O'Leary CJ, *et al.* Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J* 1997; 10: 1754–1760.
3. Anzueto A. Impact of exacerbations on COPD. *Eur Respir Rev* 2010; 19: 113–118.
4. Pasteur MC, Bilton D, Hill AT, *et al.* British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65: Suppl. 1, i1–58.
5. Goeminne PC, Scheers H, Decraene A, *et al.* Risk factors for morbidity and death in non-cystic fibrosis bronchiectasis: a retrospective cross-sectional analysis of CT diagnosed bronchiectatic patients. *Respir Res* 2012; 13: 21.
6. Bott J, Moran F. Physiotherapy and NIPPV. *In:* Simonds AK, ed. Non-Invasive Respiratory Support. London: Chapman and Hall, 1995; pp. 133–142.
7. Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. *Respir Med* 2005; 99: 27–31.
8. Nicolson CH, Stirling RG, Borg BM, *et al.* The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. *Respir Med* 2012; 106: 661–667.
9. Daviskas E, Anderson SD, Gomes K, *et al.* Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. *Respirology* 2005; 10: 46–56.
10. Gjoerup J, Hilberg O, Bendstrup E. Inhaled mannitol in the treatment of non-cystic fibrosis bronchiectasis in adults. *Respirology* 2012; 17: 927–932.
11. Wills P, Greenstone M. Inhaled hyperosmolar agents for bronchiectasis. *Cochrane Database Syst Rev* 2006; 2: CD002996.
12. Bradley J, Moran F, Greenstone M. Physical training for bronchiectasis. *Cochrane Database Syst Rev* 2002; 3: CD002166.
13. Liaw MY, Wang YH, Tsai YC, *et al.* Inspiratory muscle training in bronchiectasis patients: a prospective randomized controlled study. *Clin Rehabil* 2011; 25: 524–536.
14. Naraparaju S, Vaishali K, Venkatesan P, *et al.* A comparison of the Acapella and a threshold inspiratory muscle trainer for sputum clearance in bronchiectasis – a pilot study. *Physiother Theory Pract* 2010; 26: 353–357.
15. Figueiredo PH, Zin WA, Guimarães FS. Flutter valve improves respiratory mechanics and sputum production in patients with bronchiectasis. *Physiother Res Int* 2012; 17: 12–20.
16. Crockett AJ, Cranston JM, Latimer KM, *et al.* Mucolytics for bronchiectasis. *Cochrane Database Syst Rev* 2001; 1: CD001289.
17. Furumoto A, Ohkusa Y, Chen M, *et al.* Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. *Vaccine* 2008; 26: 4284–4289.
18. Chang CC, Singleton RJ, Morris PS, *et al.* Pneumococcal vaccines for children and adults with bronchiectasis. *Cochrane Database Syst Rev* 2009; 2: CD006316.
19. Lasserson T, Holt K, Greenstone M. Oral steroids for bronchiectasis (stable and acute exacerbations). *Cochrane Database Syst Rev* 2001; 4: CD002162.
20. Tsang KW, Tan KC, Ho PL, *et al.* Inhaled fluticasone in bronchiectasis: a 12 month study. *Thorax* 2005; 60: 239–243.
21. Kapur N, Bell S, Kolbe J, *et al.* Inhaled steroids for bronchiectasis. *Cochrane Database Syst Rev* 2009; 1: CD000996.
22. Martinez-García MA, Perpiñá-Tordera M, Román-Sánchez P, *et al.* Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. *Respir Med* 2006; 100: 1623–1632.
23. Shinkai M, Henke MO, Rubin BK. Macrolide antibiotics as immunomodulatory medications: proposed mechanisms of action. *Pharmacol Ther* 2008; 117: 393–405.
24. Anwar GA, Bourke SC, Afolabi G, *et al.* Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis. *Respir Med* 2008; 102: 1494–1496.
25. Wong C, Jayaram L, Karalus N, *et al.* Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012; 380: 660–667.

26. Wilson R, Wells AU. Azithromycin in bronchiectasis: when should it be used? *Lancet* 2012; 380: 627–629.
27. Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis in children and adults. *Cochrane Database Syst Rev* 2007; 2: CD001392.
28. Tsang KW, Ho PI, Chan KN, *et al.* A pilot study of low-dose erythromycin in bronchiectasis. *Eur Respir J* 1999; 13: 361–364.
29. Hill SL, Burnett D, Hewetson KA, *et al.* The response of patients with purulent bronchiectasis to antibiotics for four months. *Q J Med* 1988; 66: 163–173.
30. Chalmers JD, Smith MP, McHugh BJ, *et al.* Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2012; 186: 657–665.
31. Angrill J, Agustí C, De Celis R, *et al.* Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. *Am J Respir Crit Care Med* 2001; 164: 1628–1632.
32. Angrill J, Agustí C, de Celis R, *et al.* Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. *Thorax* 2002; 57: 15–19.
33. Frederiksen B, Lanng S, Koch C, *et al.* Improved survival in the Danish center-treated cystic fibrosis patients: results of aggressive treatment. *Pediatr Pulmonol* 1996; 21: 153–158.
34. Mandal P, Sidhu MK, Donaldson LS, *et al.* Eight-weekly intravenous antibiotics is beneficial in severe bronchiectasis. *QJM* 2013; 106: 27–33.
35. Ratjen F, Munck A, Kho P, *et al.* Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE Trial. *Thorax* 2010; 65: 286–291.
36. Drobnic ME, Suñé P, Montoro JB, *et al.* Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginos*a. *Ann Pharmacother* 2005; 39: 39–44.
37. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest* 2005; 127: 1420–1426.
38. Steinfort DP, Steinfort C. Effect of long-term nebulized colistin of lung function and quality of life in patients with chronic bronchial sepsis. *Intern Med J* 2007; 37: 495–498.
39. Dhar R, Anwar GA, Bourke SC, *et al.* Efficacy of nebulised colomycin in patients with non-cystic fibrosis bronchiectasis colonised with *Pseudomonas aeruginosa*. *Thorax* 2010; 65: 553.
40. McCoy KS, Quittner AL, Oermann CM, *et al.* Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Respir Crit Care* 2008; 178: 921–928.
41. Wilson R, Welte T, Polverino E, *et al.* Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. *Eur Respir J* 2013; 41: 1107–1115.
42. Murray MP, Govan JR, Doherty CJ, *et al.* A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2011; 183: 491–499.
43. Antoniu SA, Trofor AC. Inhaled gentamicin in non-cystic fibrosis bronchiectasis: effects of long-term therapy. *Expert Opin Pharmacother* 2011; 12: 1191–1194.
44. Ho PL, Chan KN, Ip MS, *et al.* The effect of *Pseudomonas aeruginosa* infection on clinical parameters in steady-state bronchiectasis. *Chest* 1998; 114: 1594–1598.
45. Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, *et al.* Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007; 132: 1565–1572.
46. Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009; 4: CD004197.
47. Davies G, Wells AU, Doffman S, *et al.* The effect of *Pseudomonas aeruginosa* on pulmonary function in patients with bronchiectasis. *Eur Respir J* 2006; 28: 974–979.
48. White L, Mirrani G, Grover M, *et al.* Outcomes of *Pseudomonas* eradication therapy in patients with non-cystic fibrosis bronchiectasis. *Respir Med* 2012; 106: 356–360.
49. Lasserson T, Holt K, Evans D, *et al.* Anticholinergic therapy for bronchiectasis. *Cochrane Database Syst Rev* 2001; 4: CD002163.
50. Sheikh A, Nolan D, Greenstone M. Long-acting β2-agonists for bronchiectasis. *Cochrane Database Syst Rev* 2001; 4: CD002155.
51. Corless JA, Warburton CJ. Leukotriene receptor antagonists for non-cystic fibrosis bronchiectasis. *Cochrane Database Syst Rev* 2000; 4: CD002174.
52. Steele K, Greenstone M, Lasserson JA. Oral methyl-xanthines for bronchiectasis. *Cochrane Database Syst Rev* 2001; 1: CD002734.
53. Pizzutto SJ, Upham JW, Yerkovich ST, *et al.* Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis. *Cochrane Database Syst Rev* 2010; 4: CD007525.
54. Corless JA, Warburton CJ. Surgery *vs* non-surgical treatment for bronchiectasis. *Cochrane Database Syst Rev* 2000; 3: CD002180.
55. Sharples LD, Edmunds J, Bilton D, *et al.* A randomised controlled crossover trial of nurse practitioner *versus* doctor led outpatient care in a bronchiectasis clinic. *Thorax* 2002; 57: 661–666.
56. Chalmers JD, McHugh BJ, Docherty C, *et al.* Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. *Thorax* 2013; 68: 39–47.
57. Patel IS, Vlahos I, Wilkinson TM, *et al.* Bronchiectasis, exacerbation indices, and inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 170: 400–407.

58. O'Brien C, Guest PJ, Hill SL, *et al.* Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000; 55: 635–642.
59. Anthonisen NR, Manfreda J, Warren CP, *et al.* Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196–204.
60. Kapur N, Masters IB, Chang AB. Exacerbations in noncystic fibrosis bronchiectasis: clinical features and investigations. *Respir Med* 2009; 103: 1681–1687.
61. Finklea JD, Khan G, Thomas S, *et al.* Predictors of mortality in hospitalized patients with acute exacerbation of bronchiectasis. *Respir Med* 2010; 104: 816–821.
62. Hoffken G, Lorenz J, Kern W, *et al.* Epidemiologie, Diagnostik, antimikrobielle Therapie und Management von erwachsenen Patienten mit ambulant erworbenen unteren Atemwegsinfektionen sowie ambulant erworbener Pneumonie Update 2009. S3-Leitlinie der Paul-Ehrlich-Gesellschaft fur Chemotherapie, der Deutschen Gesellschaft fur Pneumologie und Beatmungsmedizin, der Deutschen Gesellschaft fur Infektiologie und vom Kompetenznetzwerk CAPNETZ [Epidemiology, diagnosis, antimicrobial therapy and management of community-acquired pneumonia and lower respiratory tract infections in adults. Guidelines of the Paul-Ehrlich-Society for Chemotherapy, the German Respiratory Society, the German Society for Infectiology and the Competence Network CAPNETZ Germany]. *Pneumologie* 2009; 63: e1–e68.
63. Pletz MW, McGee L, Burkhardt O, *et al.* Ciprofloxacin treatment failure in a patient with resistant *Streptococcus pneumoniae* infection following prior ciprofloxacin therapy. *Eur J Clin Microbiol Infect Dis* 2005; 24: 58–60.
64. Pines A, Raafat H, Siddiqui GM, *et al.* Treatment of severe pseudomonas infections of the bronchi. *Br Med J* 1970; 1: 663–665.
65. Pines A, Khaja G, Raafat H, *et al.* Preliminary clinical experience with ticarcillin (BRL 2288) in 101 patients treated for severe respiratory infections. *Chemotherapy* 1974; 20: 39–44.
66. Bilton D, Henig N, Morrissey B, *et al.* Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 2006; 130: 1503–1510.
67. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax* 1995; 50: 604–609.
68. Holland AE, Denehy L, Ntoumenopoulos G, *et al.* Non-invasive ventilation assists chest physiotherapy in adults with acute exacerbations of cystic fibrosis. *Thorax* 2003; 58: 880–884.
69. Young AC, Wilson JW, Kotsimbos TC, *et al.* Randomised placebo controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. *Thorax* 2008; 63: 72–77.
70. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev* 2009; 1: CD002769.
71. Flight WG, Shaw J, Johnson S, *et al.* Long-term non-invasive ventilation in cystic fibrosis – experience over two decades. *J Cyst Fibros* 2012; 11: 187–192.

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Educational questions

1. What are the most common pathogens associated with bacterial infections in patients with chronic bronchitis?

❑ Nontypeable *Haemophilus influenzae*. ❑ *Streptococcus pneumoniae*. ❑ *Moraxella catarrhalis*. ❑ None of the above. ❑ All of the above.

2. Patient with chronic bronchitis are at risk for:

❑ More exacerbations. ❑ Increased hospitalisations. ❑ Progressive decline in lung function. ❑ None of the above. ❑ All of the above.

3. What medications have been shown to prevent exacerbations in patients with chronic bronchitis?

❑ Roflumilast. ❑ Azithromycin, 500 mg three times per week. ❑ Ipratropium, one puff twice a day. ❑ All of the above. ❑ None of the above.

4. Which of the following statements is true about sputum purulence?

❑ It is due to the presence of dead neutrophils. ❑ It indicates bronchial colonisation. ❑ It indicates an inflammatory response. ❑ It can be reliably communicated by the patient. ❑ All of the above. ❑ None of the above.

Continued on next page

5. Which one of the following statements is false about the presence of sputum purulence?
❑ It indicates an Anthonison type 1 exacerbation. ❑ It reflects the need for antibiotics. ❑ It can be a feature of the stable state. ❑ It suggests the presence of bronchiectasis.

6. Which of the following is/are true about mucoid sputum? (Select all that apply)
❑ It indicates that an exacerbation is unlikely. ❑ It is usually sterile. ❑ It indicates that bronchial inflammation is absent. ❑ It predicts a likely frequent exacerbator. ❑ It is a clear indication for withholding antibiotic therapy.

7. Which bacterial species is not considered a potentially pathogenic microorganism?
❑ *Pseudomonas aeruginosa*. ❑ Nontypeable *Haemophilus influenzae*. ❑ *Staphylococcus aureus*.
❑ *Streptococcus viridans*. ❑ *Klebsiella pneumoniae*.

8. Which pathophysiological mechanisms are involved in the pathogenesis of bacterial COPD exacerbations?
❑ Acquisition of new strains of bacteria. ❑ Antigenic changes in pre-existing bacterial strains. ❑ Increase in the bronchial bacterial load. ❑ None of the above. ❑ All of the above.

9. What are the risk factors for chronic bronchial infection in COPD?
❑ Positive smoking history. ❑ Impaired lung function. ❑ Bronchiectasis. ❑ High-dose inhaled corticosteroid use. ❑ All of the above.

10. With respect to chronic bronchial infection (CBI), which statement is incorrect?
❑ It induces local and systemic inflammatory response. ❑ It has been associated with accelerated lung function decline. ❑ In *Pseudomonas aeruginosa* CBI, the term colonisation is preferred to CBI. ❑ It has been associated with higher exacerbation frequency. ❑ It has been postulated that it may contribute to the accelerated atherosclerosis in COPD patients.

11. Which of the following species is not a usual coloniser in COPD?
❑ *Klebsiella pneumoniae*. ❑ *Pseudomonas aeruginosa*. ❑ *Moraxella catarrhalis*. ❑ *Streptococcus pneumoniae*.
❑ *Haemophilus influenzae*.

12. What is the definition of exacerbation of COPD?
❑ An acute event characterised by an increase in sputum volume and purulence that is beyond normal day-to-day variations. ❑ An acute event characterised by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. ❑ An acute event characterised by an increase in respiratory symptoms that is beyond normal day-to-day variations.

13. How is a severe COPD exacerbation defined?
❑ Exacerbation requiring hospitalisation. ❑ Exacerbation requiring oxygen therapy. ❑ Exacerbation requiring antibiotic treatment.

14. Patients with frequent exacerbations show which one of the following?
❑ An increase in plasma fibrinogen over time. ❑ A decrease in plasma fibrinogen over time. ❑ A consistent increase in C-reactive protein in bronchoalveolar lavage.

15. Exacerbations are associated with:
❑ Pulmonary function decline. ❑ Mortality. ❑ Costs. ❑ All of the above.

16. Troponin T in COPD patients hospitalised because of an exacerbation is an:
❑ Independent prognostic factor for mortality after discharge. ❑ Independent prognostic factor for in-hospital failure. ❑ Independent prognostic factor for stroke.

17. A patient with stage III COPD and a history of chronic cardiac disease presents with a COPD exacerbation. He reports no previous hospital admissions. This patient should be treated with:
❑ Trimethoprim/sulfamethoxazole. ❑ Amoxycillin/clavulanate. ❑ Doxycycline. ❑ Azithromycin.

18. Which patient may not receive antibiotic treatment for acute exacerbations in COPD (AECOPD)?
❑ A patient with FEV_1:50% who presents with increased dyspnoea, cough and fever. ❑ A patient who is admitted to the intensive care unit. ❑ A patient with FEV_1:40% who presents with dyspnoea and purulent expectoration. ❑ A patient who reports three hospitalisations for AECOPD during the last year.

19. Which is the most common bacterial pathogen isolated in COPD exacerbations?
❑ *Streptococcus pneumoniae*. ❑ *Moraxella catarrhalis*. ❑ *Haemophilus influenzae*. ❑ *Mycoplasma pneumoniae*.

20. Which is the indicated antibiotic treatment for a patient with severe COPD who is admitted to the hospital due to an acute exacerbation in COPD and reports history of Crohn's disease and systemic use of prednisolone (15 mg daily)?
❑ Azithromycin. ❑ Amoxycillin/clavulanate. ❑ Levofloxacin 750 mg per day. ❑ Ceftriaxone.

21. Which changes on high-resolution computed tomography in bronchiectasis commonly reverse with treatment? (Select all that apply)
❑ Exudative bronchiolitis (tree-in-bud). ❑ Mucus plugging. ❑ Volume loss. ❑ Bronchial dilatation.
❑ Bronchial wall thickening.

22. Which conditions causing bronchiectasis most commonly affect the upper lobes? (Select all that apply)
❑ Allergic bronchopulmonary aspergillosis. ❑ Primary ciliary dyskinesia. ❑ Rheumatoid arthritis.
❑ *Mycobacterium avium* complex infection. ❑ Cystic fibrosis.

23. Which statements about primary ciliary dyskinesia are true? (Select all that apply)
❑ Males are always infertile. ❑ Dextracardia is present in most patients. ❑ Neonates can present with respiratory distress. ❑ Cilia can have a normal beat frequency. ❑ Cilia can have a normal ultrastructure.

24. Which of the following statements about high-resolution computed tomography and bronchiectasis are true? (Select all that apply)
❑ Tree-in-bud exudative bronchiolitis is the most prominent feature of diffuse panbronchiolitis.
❑ Nontuberculous mycobacterial infection is a common cause of severe bronchiectasis. ❑ Middle lobe bronchiectasis commonly occurs in idiopathic cases. ❑ Williams–Campbell syndrome describes bronchiectasis caused by bronchial obstruction due to extrinsic compression by enlarged lymph nodes.
❑ In primary ciliary dyskinesia bronchiectasis is often most severe in the middle lobes.

25. Which of the following nontuberculous mycobacterial species are regarded as potentially pathogenic? (Select all that apply)
❑ *Mycobacterium avium* complex. ❑ *Mycobacterium fortuitum*. ❑ *Mycobacterium gordonae*.
❑ *Mycobacterium xenopi*. ❑ *Mycobacterium interjectum*.

Continued on next page

26. With respect to allergic bronchopulmonary aspergillosis, which one of the following statements is false?

❑ Fleeting consolidation is typical on serial chest radiographs. ❑ The density of mucus plugs on high-resolution computed tomography may be strikingly higher than water density. ❑ There is a higher prevalence of aspergillus lung disease in bronchiectasis patients with nontuberculous mycobacterial infection. ❑ Upper lobe varicose bronchiectasis is typical. ❑ It is one of the commonest causes of bronchiectasis.

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Print ISSN 1025-448x
Online ISSN 2075-6674
Print ISBN 978-1-84984-034-7
Online ISBN 978-1-84984-035-4

Number 60 June 2013
£45.00/€53.00/US$80.00

ISBN 978-1-84984-034-7